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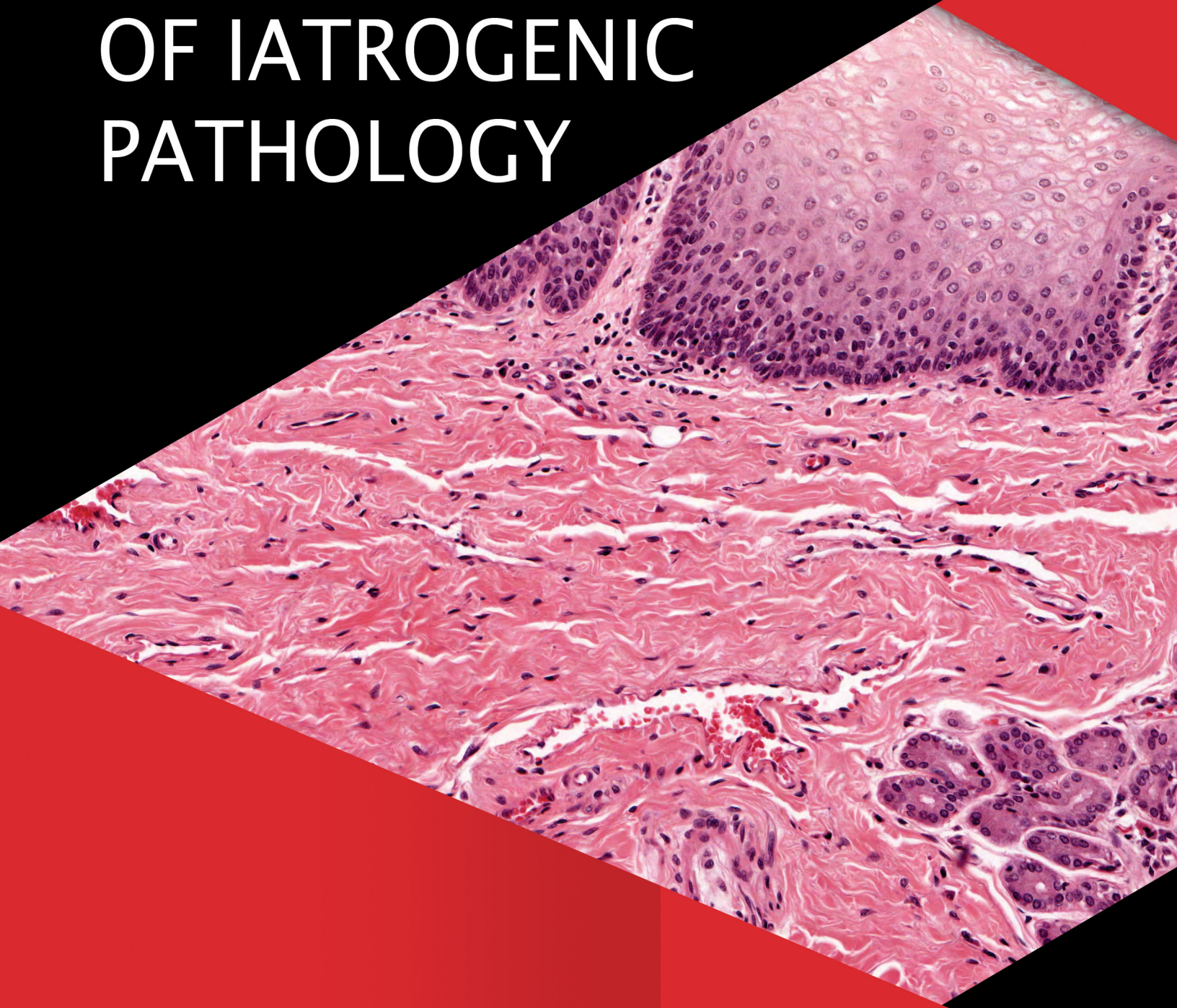
TEXTBOOK OF IATROGENIC PATHOLOGY



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Textbook of Iatrogenic Pathology

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FOREWORD

The Textbook of Iatrogenic Pathology represents a transdisciplinary collection of the main effects of drugs and medical interventions encountered in daily practice. It is edited by two pathologists with significant experience in autopsy who are also teaching the under- and postgraduate students in field of iatrogenic pathology.

The book is split in two parts. The first part that comprises 13 chapters was mainly synthesized by pathologists based on the literature data and practical aspects observed during daily autopsies. In the 6 chapters of the second part, the doctors involved in the clinical practice have presented the specific aspects of their surgical or medical specialties.

This book is a necessity for all persons involved in the patient's care, from student to professor and represents at the moment the largest collection of aspects related to iatrogenic pathology. It is an original and complex book that include the newest aspect of iatrogenesis. It is always important to learn all our life not only from direct/positive evidences, but also from missing facts or/and medical errors.

I strongly recommend publication of the Textbook of Iatrogenic Pathology as a necessity for awareness of medical staff in the field of consequences of the medical facts.

Prof. Marius Raica
Rector of the University of Medicine and Pharmacy,
Timisoara,
Romania

PREFACE

The Textbook of Iatrogenic Pathology concerns doctors and medications. Iatrogenic is a word that derives from the Greek “iatros”, which means “doctor” or “medicine”, and “genic”, which means “induced by”. Thus, the book comprises a basic synthesis of the consequences of medical diagnostic or therapeutic procedures, as well as the main side effects of medications in daily use.

In the present book, the authors aimed to present the interdisciplinary features of iatrogenic lesions. The book is based on the opinions of doctors from several disciplines, including pathology, surgery, intensive care, neurology, metabolic diseases, *etc*. In reviewing the existing literature, we did not find complex studies or large syntheses in this field, and therefore consider this book to be very useful to clinicians of all medical specialties. Moreover, the co-editor of the book founded the Department of Iatrogenic Pathology in our university and we offer, every year, lectures in this field for medical students (MD students, dental medicine students and nurses). Our practical experience (editor and co-editor) based on the lectures and everyday autopsies (we perform more than 200 autopsies per year), along with collaboration with clinicians, guarantees the complexity and originality of the present book.

The book is organized into two main parts. The first (13 chapters) is written by pathologists and describes iatrogenic lesions (adverse drug reactions, lesions occurring during diagnosis and as consequences of therapeutic interventions) of the organs and systems. These chapters include practical examples from our daily practice in the Department of Pathology. The second part (six chapters) is written by clinicians and describes specific lesions induced by surgery, neurology, *etc.*

The following main chapters will be included: adverse drug reactions; radiation-induced lesions (through radiotherapy); iatrogenic immunopathology (including pathology regarding organ and tissue transplantation); iatrogenic lesions of the cardiovascular system; iatrogenic lesions of the lung and airways; iatrogenic lesions of the digestive tract (mouth, pharynx, esophagus, stomach, small and large bowel); iatrogenic lesions of the peritoneum and abdominal cavity; iatrogenic lesions of the liver, bile ducts and pancreas; iatrogenic lesions of the kidney and urinary tract; iatrogenic lesions of the female genital organs and breast; iatrogenic lesions of the male genital organs; iatrogenic lesions of the bone marrow and lymphoid tissue; iatrogenic lesions of cutaneous tissue; iatrogenic lesions in endocrinology; iatrogenic lesions in neurology; iatrogenic lesions in anesthesiology and intensive care; iatrogenic lesions in general and thoracic surgery; iatrogenic lesions in gynecology and obstetrics; and iatrogenic lesions in neurosurgery.

This book is for those who already have a basic understanding of the mysteries of the human body and have decided that they are ready to treat it. It is for young residents who believe that they already know all about medicine and its pitfalls. If you decide to read it, try to perform a self-assessment of your medical aptitudes. If you feel that the medical mistakes outlined here can easily occur, try to discover how they can be prevented. If you feel that they cannot happen to you, try to read more on the subject.

Finally, do not forget that honesty is a doctor’s best policy and that the real physician is one who chooses to learn, to study, to be informed and to collaborate with his/her colleagues.

To treat and help others, to be a doctor, can be a pleasure and can be a challenge, but it is also a daily choice. From time to time, a doctor cannot treat or help a given patient, and may make mistakes. This is a reality. To judge, to know, to think, to ask – these are the grounding secrets of a physician, and are mandatory to prevent mistakes becoming habits.

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ABBREVIATIONS

5-FU = 5-fluorouracil
ACE = angiotensin-converting enzyme
ADR = adverse drug reaction
AGEP = acute generalized exanthematous pustulosis
AIH = amiodarone-induced hypothyroidism
AIT = amiodarone-induced thyrotoxicosis
ALI = acute lung injury
AMP = cyclic adenosine monophosphate
AMPK = adenosine monophosphate-activated protein kinase
ARDS = acute respiratory distress syndrome
ASCUS = atypical squamous cells of undetermined significance
ATLS = advanced trauma life support
ATP = adenosine triphosphate
BBB = blood-brain barrier
BCG = Bacillus Calmette–Guerin
BMI = body mass index
BMS = bare metal stent
BPH = benign prostatic hyperplasia
BVS = bioresorbable vascular scaffold
CBD = common bile duct
CBG = corticosteroid-binding globulin
CIN = cervical intraepithelial neoplasia
CK = creatine kinase
CMV = cytomegalovirus
CN = Consciousness
CNS = central nervous system
COPD = chronic obstructive pulmonary disease
CSF = cerebrospinal fluid
CT = computed tomography
CTP = corticotroph tumor progression
CU-ADR = cutaneous adverse drug reaction
CYP3A4 = cytochrome-oxidase 3A4

D_2 receptor = dopaminergic receptor 2
DCO = damage control orthopedics
DES = drug eluting stent
DETA = Diethylenetriamine
DHEA = dehydroepiandrosterone
DIC = disseminated intravascular coagulation
DIND = drug-induced neurological disorders
DM = diabetes mellitus
DRBA = dopamine receptor-blocking agent
DRESS = drug reaction with eosinophilia and systemic symptoms
EBV = Epstein-Barr virus
ECG = electrocardiogram
EEG = electroencephalography
EGF = epidermal growth factor
EGFR = epidermal growth factor receptor
EMA = European Medicines Agency
EORTC = European Organization for Research and Treatment of Cancer
EP = encephalopathy
ePTFE = polytetrafluoroethylene
EPPER = eosinophilic, polymorphic and pruritic eruption associated with radiotherapy
EQ-5D = EuroQol five dimensions questionnaire
ERC = European Resuscitation Council
ERCP = endoscopic retrograde cholangiopancreatography
ESR = erythrocytes sedimentation rate
EUS = endoscopic ultrasonography
FAP = Familial Adenomatous Polyposis
FDA = Food and Drug Administration
FEF = forced expiratory flow
FEV = forced expiratory volume
FGF = fibroblast growth factor
FGS = female genital system
FNA = fine needle aspiration
FRC = functional residual capacity
FSH = follicle stimulating hormone

GAPPS = gastric proximal polyposis of the stomach
GAVE = gastric antral vascular ectasia
GERD = gastro esophageal reflux disease
GH = growth hormone
GI = gastrointestinal
GnRH = gonadotropin-releasing hormone
HBV = hepatitis B virus
HCC = hepatocellular carcinoma
HCV = hepatitis C virus
HE = Hematoxylin-Eosine
HHV = human herpes virus
HIV = human immunodeficiency virus
HLA = human leukocyte antigen
HPV = human papilloma virus
H-SIL = high-grade squamous intraepithelial lesion
HTLV = human T-cell lymphotropic virus
HV = herpes virus
IBD = inflammatory bowel disease
ICU = Intensive Care Unit
Ig = immunoglobulin
IL = interleukins
IR = insulin-resistance
ITP = idiopathic thrombocytopenic purpura
IUD = intrauterine device
JCV = John Cunningham polyomavirus
JGCA = Japanese Gastric Cancer Association
LG = lethargy
LKB1 = liver kinase B1
LSD = Lysergic acid diethylamide
L-SIL = Low-grade squamous intraepithelial lesion
MDMA = 3,4-Methylenedioxymethamphetamine
MET = mesenchymal-epithelial transition
MRCP = magnetic resonance cholangiopancreatography
MRI = magnetic resonance imaging
MS = muscular system

MSOF = multisystem organ failure
mTOR = mammalian target of rapamycin
mTORC1 = mammalian TOR-complex 1
NAION = non-arteritic ischemic optic neuropathy
Nd:YAG = neodymium-doped YAG
NGAL = neutrophil gelatinase-associated lipocalin
NHLBI = National Heart, Lung and Blood Institute
NMJ = neuromuscular junction
NO = nitrogen monoxide
NS = non-specific
NSAIDs = non-steroidal anti-inflammatory drugs
PCI = Percutaneous Coronary Intervention
PDE = phosphodiesterase
PDGF = platelet-derived growth factor
PEEP = positive-end expiratory pressure
PML = Progressive multifocal leukoencephalopathy
PNS = peripheral nervous system
PONV = postoperative nausea and vomiting
PPAR = peroxisome proliferator-activated receptor
PPI = proton pump inhibitor
PRL = prolactin
PTCA = Percutaneous Coronary Angioplasty
RET = rearranged during transfection
rhGH = recombinant human-type growth hormone
RTOG = Radiation Therapy Oncology Group
SIADH = syndrome of inappropriate antidiuretic hormone secretion
SIL = squamous intraepithelial lesion
SIRS = systemic inflammatory response syndrome
SIRT = selective internal radiation therapy
SJS = Stevens-Johnson syndrome
SM = somnolence
SN = syncope
ST = stupor
STK11 = Serine/Threonine Kinase 11
T3 = triiodothyronine

T4 = thyroxine
TAPP = transabdominal pre-peritoneal
TEN = toxic epidermal necrolysis
TGF = transforming growth factor
TNF = tumor necrosis factor
TRAIL = tumor necrosis factor-related apoptosis-inducing ligand
TRALI = transfusion-related acute lung injury
TRH = thyrotropin-releasing hormone
TSH = thyroid stimulating hormone
TTP = Thrombotic thrombocytopenic purpura
TUR = transurethral resection
TUR-P = transurethral resection of the prostate
UK = United Kingdom
UPA = ulipristal acetate
VAS = Visual Analog Scale
VEGF = vascular endothelial growth factor
WHO = World Health Organization
Wnt = Wnt-β-catenin signaling
Y = yttrium
YAG = yttrium aluminum garnet

CHAPTER 1

Adverse Drug Reactions

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Abstract: This chapter includes general aspects regarding the definitions and mechanisms of occurrences of adverse drug reactions (ADRs). They can be realized through non-immunological (type A reaction) or immunological (type B reaction) pathways and can be dose-dependent or independent. A new type of ADR is encountered in oncology departments in patients taking monoclonal antibodies. It is known as drug-induced apoptosis and is presented in this chapter. The mechanisms and classification of the severity of these reactions, as well as the particularities of acute, chronic and chronic-delayed ADRs, are also explored. The severity can be patient- or drug-related. In the chapters that follow, specific system- and organ-related ADRs are presented.

Keywords: Acute, Adverse drug reaction, Allergy, Apoptosis, Ahronic, Hypersensitivity, Iatrogenic, Idiosyncrasy, Monoclonal antibodies, Recurrent.

INTRODUCTION

Adverse drug reactions (ADRs) are defined as unwanted reactions associated with drug intake [1]. According to the World Health Organization (WHO), an ADR is defined as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or treatment of disease, or for the modification of physiological function" [1]. It has been estimated that ADRs are associated with 10-20% of all drugs, yet the real incidence is unknown and the importance of these side effects is often underestimated [2, 3].

Based on their severity, ADRs are classified as low, moderate or severe, and can have a lethal evolution. The Food and Drug Administration (FDA) considers a serious adverse event to be one that impacts the patient's outcome in one the following ways: leads to a threat to the patient's life or induces the patient's death; leads to prolonged hospitalization; gives rise to a congenital anomaly (in pregnant females); or induces disability or requires supplementary interventions

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to avoid permanent disability [4]. The main ADRs that can induce the patient's death are the following: fulminant bleeding from an iatrogenic peptic ulcer or occurring as a side effect of anticoagulant or chemotherapeutic drugs, severe aplastic anemia, hepatorenal failure, septic shock, anaphylactic shock, *etc*. [5].

In the United States, it has been estimated that approximately 3-7% of all hospital admissions are due to an ADR [6], 10-20% of which are severe [7]. The incidence of ADR-induced mortality is about 0.5-0.9%, but this is known to be an underestimate [8].

An ADR is a multifactorial process that can affect the skin, liver, kidneys, bone marrow, blood vessels, gastrointestinal (GI) tract, lungs and other organs and tissues. In this chapter, basic features regarding ADRs are presented, while system- or organ-related reactions are included in the following chapters of this book.

Types and Mechanisms of ADRs

Based on the ***time of appearance***, ADRs are classified as acute, chronic or chronic-delayed reactions. They occur during a single dose or a single cycle of therapy (*acute ADRs*), or can be dose- and time-related. A drug-induced reaction that occurs after 10-12 months of treatment is considered a *chronic ADR,* whereas *chronic-delayed* effects are realized years after treatment. *Recurrent ADRs* can also be identified in clinical practice [9].

Regarding the ***mechanism of occurrence***, in 1977 it was observed that ADRs could be *pharmacologically-induced (type A)* or the result of *idiosyncratic lesions (type B)* [10]. The most common ADRs (80%) are type A reactions that are dose-dependent and can be reversible after drug cessation [7, 11]. About 75-80% of type A reactions are predictable [11]. Type B reactions are immune-mediated, cannot be predicted, are dose-independent and occur only in susceptible individuals [1, 7].

Based on their mechanisms, ADRs are also classified as specific (immune mechanisms and nonallergic hypersensitivity) and non-specific. *Non-specific or non-immunological reactions (type A)* can be induced by overdose, direct side effects or drug interactions [1, 12]. The toxic effect can be dose-dependent or a result of metabolic disorders (slow hepatic detoxification) or renal failure (delayed elimination). Non-medical drug overdose, whether accidental or intentional, is not considered an ADR. Pharmacological side effects refer to drug-induced disorders at therapeutic doses [12].

In hospitalized patients, sedatives and hypnotics, respectively opiates and narcotics, are considered the leading sources of ADRs, followed by steroids, antibiotics and anticoagulants. As a result of drug interaction, a specific effect of a medical agent can be diminished or amplified. For example, barbiturates such as phenobarbital can diminish other drug effects as a result of hepatic enzymes activation. The antibiotic drug rifampin accelerates the renal elimination of drugs used in cardiology, such as verapamil. The histamine receptor antagonist cimetidine affects the metabolism and inhibits the excretion of several drugs, such as the antimalarial hydroxychloroquine, psychoactive medications and nifedipine, and doubles the half-life of zolmitriptan (used for migraine attacks) [5].

A distinct mechanism of non-immunological ADRs is *drug-induced apoptosis*. This is specific to the latest monoclonal antibodies used in medical oncology for individualized treatment (*e.g.*, bevacizumab, rituximab, adalimumab, cetuximab, trastuzumab, *etc.*) and other drugs such as the anti-acne isotretinoin (13-ci--retinoic acid). Apoptosis is a consequence of drug-induced formation of apoptotic protein tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and neutrophil gelatinase-associated lipocalin (NGAL). Due to the risk of teratogenicity, oligohydramnios and poor neonatal outcomes, these drugs are not recommended for use during pregnancy. In animals, drug-induced apoptosis has been proven to decrease hypothalamic cell numbers and to induce depression [13, 14].

Specific or immunological reactions (type B) are dose-independent, difficult to predict and occur at doses tolerated by normal subjects. They include immune-mediated lesions and nonallergic hypersensitivity [1, 11].

Nonallergic or pseudoallergic hypersensitivity which is also known as idiosyncrasy or intolerance, is defined as the unusual or unpredictable effect that might be induced in a particular patient at usual doses as a result of enzymatic deficiency or through a genetic mechanism [1]. It can be a life-threatening disorder.

Immune mechanisms or allergic (IgE-mediated and non-IgE-mediated) hypersensitivity reactions are the result of activation of one of the four hypersensitivity reactions: type I (IgE-mediated), type II (cytotoxic), type III (immune complex) or type IV (cell-mediated) [1, 5, 11]. Anaphylactic reactions (type I hypersensitivity) can be mild, moderate or severe (anaphylactic shock) and are not dose-dependent. They are realized as cutaneous eruptions, fever, eosinophilic pneumonia and, infrequently, thrombocytopenia and anemia. Other rare manifestations of allergies are vasculitis (*e.g.*, penicillin, sulfonamides, iodine, *etc.*), interstitial nephritis (methicillin) and hepatic injury [5]. Cytotoxic

CHAPTER 2

Radiation-Induced Lesions

Simona Gurzu* and **Ioan Jung**

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Abstract: This chapter includes general aspects regarding the mechanisms of radiation-induced lesions and specific organ-related effects of radiotherapy, from the cardiovascular system to bone marrow. For oncologists, understanding the mechanisms of radiation-induced carcinogenesis and knowing the estimated time taken for post-radiotherapy occurrence of metachronous tumors is mandatory for proper patient follow-up. We here analyze all lesions of the skin and internal organs, leaving aside tumors for this chapter. The acute and chronic effects of radiotherapy are presented in detail, and the grading system of oral mucositis is also outlined.

Keywords: Actinic enterocolitis, Bone marrow, Bronchiolitis obliterans, Dermatitis, Endarteritis obliterans, EPPER-syndrome, Iatrogenic, Malignancy, Mucositis, Pneumonitis, Radiation enteropathy, Radiodermatitis, Radiotherapy, Reticuloid syndrome, Sweet's syndrome, Vasculitis.

INTRODUCTION

In medical practice, radiation is used for diagnosis (0.1-10 mSv per procedure) or therapeutic purposes (20-60 Gy per targeted tissue). Two types of ionizing radiation are used for radiotherapy: photon radiation (X- or gamma-rays) and particle radiation (electrons, protons, neutrons, carbon ions, alpha and beta particles). Photon radiation is used for deep tumors, while electron beams are produced by a linear accelerator and are useful for treatment of cutaneous tumors and cancers that are close to the surface of the body. Proton beam radiation therapy requires highly advanced equipment and is not performed in all oncology departments. Neutron beams are useful for head, neck and prostate carcinomas, as well as for inoperable tumors. Their use severely affects the surrounding normal tissue. For radio resistant tumors, carbon ion radiation (heavy ion radiation) can be helpful. Alpha and beta particles are contained in radioactive particles that can be injected, swallowed or inserted into the body [1].

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Radiotherapy using photon radiation can involve the whole human body (*e.g.,* bone marrow transplant) but, in most cases, is used for localized therapy. Based on the radiation source, radiotherapy is classified into two main groups: external beam radiotherapy (wherein the X-ray tube is placed outside the patient's body) and brachytherapy (wherein irradiation is performed using an isotope, such as cadmium-226, cesium-137, iridium-192, iodine-125 or carbon ion, that is inserted into a tumor or within a cavity). Several medical procedures that involve radiation, such as stereotactic surgery, intensity-modulated radiation therapy, accelerated/hypo- or hyper-fractioned whole- or partial-breast irradiation, brachytherapy, intraoperative radiation therapy and fluoroscopic-guided procedures are responsible for iatrogenic lesions that range from minimal damage to chronic injuries, carcinogenic effects and radiation-induced death [2 - 7].

EFFECTS OF RADIATION – GENERAL DATA

Ionizing radiation causes DNA damage *via* direct toxicity with DNA breakage and subsequent cellular death. The indirect mechanism is based on the radiation-induced formation of free radicals with further fragmentation of the DNA or ionization of water or other molecules within the cell. The damaged tissues and vessels are then replaced by fibrocytes that are unable to synthesize collagen [8, 9].

Mucosal injuries consist of inflammatory reactions. In first steps, they are characterized by the death of mucosal cells, the breakdown of the mucosal homeostasis and the activation of pro-inflammatory cytokines, chemokines and growth factors [10]. Later, fibrosis occurs as a result of the activation of interleukins (IL-6, IL-8) and growth factors (transforming growth factor [TGF], tumor necrosis factor [TNF], *etc*.) [11, 12].

The effects of radiation depend on several factors, including the following [2, 9, 13, 14]:

- *Size of irradiation field, dose fractionation and total dose*: in the whole body, irradiation of 100-300 rad can induce acute radiation sickness, while higher doses can lead to death within approximately one month (350-500 rad) or a couple of days (>1000 rad). The main causes of death are heart/renal failure, bone marrow suppression and septicemia.
- *Exposure time and time interval between fractions:* the first effects are decreasing serum levels of erythrocytes and leukocytes (bone marrow injury), followed by mucosal damage (gastrointestinal [GI] tract injuries) and central nervous system disorders. Radiation-induced malignancy usually occurs years after radiotherapy.

- *Type and technique of irradiation*: the most aggressive form of radiation is alpha particle radiation, followed by beta radiation. X-rays have a highly penetrative effect with minimal tissular damage, but can destroy the weak bonds between nucleic acids and induce chromosomal alterations.
- *Radiation sensitivity of tissue:* hair follicles, mucosa of the GI tract, bone marrow, lymphatic tissue, ovarian follicles and testes present high sensitivity, while medium sensitivity is noted for connective tissue, blood vessels and urothelium. Cartilaginous tissue, muscles, corpus luteum and ovarian stroma are relatively radio resistant, as are the liver, kidneys, pancreas and brain.
- *Individual susceptibility*: the consequences of radiotherapy are more severe in patients who have previously received radiotherapy, and also depend on the patient's age at exposure, gender, associated comorbidities and genetic factors.

POST-RADIATION MALIGNANCY

Ionizing radiation can induce carcinogenesis. Approximately 0.5-2.2% of patients develop a histopathologically independent second tumor within 5-7 years of radiotherapy, in a dose-dependent manner. The first known instance of radiation-induced cancer was reported in 1902, on ulcerated skin, and leukemia in radiation workers was reported in 1911. Moreover, in recent history, the leukemia risk of radiologists has been found to be nine times higher than in other medical specialties, proving that whole-body radiation is a high-risk factor for bone marrow disorders [2, 13, 15, 16].

Secondary tumors are primarily located in or near the first irradiated tumor site. The most common malignant tumors are cutaneous carcinomas, carcinomas of the GI tract (30%), head and neck tumors (10%), lymphomas (10%), breast cancer (9%), sarcomas (9%) and lung cancer (8%). Radiation-induced benign tumors can also develop [2, 15, 16].

Radiotherapy performed for head, neck and mediastinal tumors can be followed by occurrence of thyroid papillary carcinoma and/or laryngeal carcinoma at 8-20 years respectively 20-40 years after radiotherapy. In 22% of the cases, the second cancer is developed in extra-laryngeal places such as lung and prostate [16, 17].

In patients with GI tract carcinomas, radiotherapy can be followed by a secondary tumor of the GI tract but extra-GI tumors such as prostate carcinoma were also reported [18]. In cases with radiation-induced damages of the pancreatic parenchyma and chronic pancreatitis, secondary neuroendocrine tumors seem to derive from the intralobular ducts lining epithelium that presents a radiation-induced endocrine differentiation [2, 19].

CHAPTER 3

Iatrogenic Immunopathology

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Abstract: This chapter covers the general aspects regarding the mechanisms of the four specific branches of iatrogenic immunopathology: iatrogenic immunodeficiencies, iatrogenic-induced lymphoproliferative diseases, hypersensitivity-induced lesions and immunopathology of transplantation. Understanding the four types of hypersensitivity reactions is mandatory for understanding the details of drug-induced lesions in organs. Mechanisms and complications of transplantation of solid organs are shown in detail.

Keywords: Adverse drug reaction, Bone marrow, Graft-versus-host disease, Host-versus-graft disease, Hypersensitivity reactions, Iatrogenic, Immunopathology, Lymphoid tissue, Lymphoproliferative disease, Rejection, Transplant.

INTRODUCTION

Iatrogenic immunopathology refers to four types of lesions: iatrogenic immunodeficiencies, iatrogenic-induced lymphoproliferative diseases, hypersensitivity-induced lesions and immunopathology of transplantation.

IATROGENIC IMMUNODEFICIENCIES

These lesions can be caused by medications, irradiation, splenectomy, surgical interventions or iatrogenic viral infections.

Drug-Induced Immunosuppression

Of all medical drugs, cytotoxic substances, steroids and immunomodulators are best known for inducing immunosuppression. Details of drug-induced bone marrow suppression are presented in Chapter 12.

***Cytotoxic Drugs*,** which are prescribed in oncotherapy and to patients with autoimmune diseases, first attack cells with rapid turnover (bone marrow cells,

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lymphoid tissue, hair follicles, *etc*.) and immunocompetent cells. Then, a decrease of the immunoglobulin synthesis rate is followed by immunodeficiency. Usually, T-cells are more resistant than B-cells. B-cell-related humoral response is abolished in early phases, followed by a decrease of T-cells-associated cellular immunity [1].

Corticosteroids are frequently used in clinical practice due to their rapid anti-inflammatory and immunosuppressive effects. They cause a decrease in the number of T-cells and, in direct contrast to cytotoxic drugs, cellular immunity is suppressed to a greater extent than is the humoral response. Immunoglobulin (Ig) synthesis is also inhibited [1].

Immunosuppressive Therapy which is especially used in transplanted recipients and patients with autoimmune disorders (*e.g.,* rheumatoid arthritis, systemic lupus erythematosus), is known to induce immunodeficiency. Primarily related to T-cells, the risk of Epstein-Barr virus (EBV) infection is increased in these patients [2, 3]. The *anti-lymphocyte serum* decreases cellular immunity and can induce anaphylaxis and/or serum sickness. *Cyclosporine* has a direct renal and hepatotoxic effect. *Calcineurin inhibitors* promote infection with oncogenic viruses, such as human papilloma virus (HPV) and herpes human virus 8 (HHV8), or exert a direct oncogenic effect. In some cases, development of lymphoproliferative disorders and tumors, such as skin cancer or Kaposi's sarcoma, were reported (*e.g.,* at two months after the initiation of immunosuppressive therapy for Wegener's granulomatosis) [4 - 6]. *Mycophenolate mofetil*, used in patients undergoing solid organ or bone marrow transplantation, can induce GI lesions in the first six months after therapy begins. Side effects include nausea, vomiting, erosions/ulcers, inflammatory bowel disease (IBD)-like disorders, colitis, abdominal pain and diarrhea. It is not nephrotoxic, like cyclosporine and tacrolimus, does not cause hyperlipidemia, as sirolimus does, and induces leukopenia less frequently than does azathioprine [7].

Radiation-Induced Immunodeficiency

Similar to the case of immunosuppressive drugs, the most radiosensitive tissues are those with high turnover, including bone marrow and lymphoid tissues, especially after irradiation of the lymph nodes (*e.g.,* Hodgkin's lymphoma). A second tumor can occur early or very late following radiotherapy (*e.g.,* sarcoma after radiotherapy for oral squamous cell carcinoma arising 16 months after completion of radiotherapy) [1, 8]. Details of radiotherapy-induced lesions are presented in Chapter 2.

Post-Splenectomy Immunodeficiency

Splenectomy is a contributing factor to infections, the most commonly involved agents being pyogenic cocci (*e.g., Streptococcus pneumoniae*) and Gram-negative bacteria. The risk of infection is higher in younger patients and those with disorders of the monocyte-macrophage system. The median time for developing an infection is about six months, ranging from one month to 50 years after splenectomy. A severe complication of patients with asplenia is progressive septicemia with fulminant and even fatal evolution. Purpura fulminans may be associated [1, 9].

Postoperative Immunodeficiency

For invasive or minimally invasive surgical techniques, the risk of postoperative fistulae, abscess formation, secondary peritonitis or sepsis should be taken into account, even in the era of modern medicine [10]. A report from 2016 revealed that, after percutaneous cholecystectomy, the risk of postoperative abscess was about 23% and the 30-day mortality rate was 9% [11]. Even following hernia repair, the risk of mesh infection remains because the foreign material acts as a biofilm and encourages bacteria proliferation [12].

Iatrogenic Viral Infection

Although rare today, infection with HIV, hepatitis viruses (HCV, HBV) or human T-cell lymphotropic virus 1 (HTLV-1) can be transmitted through blood transfusions and other parenteral exposure, or by using improperly sterilized medical equipment. In epidemic areas, the main risk factors are intramuscular/intravenous injections and contaminated blood, transplanted organs or medical and dental instruments [13 - 15].

IATROGENIC LYMPHOPROLIFERATIVE DISORDERS

These disorders can occur in transplant recipients but immunosuppressant therapy (cyclosporine, methotrexate, corticosteroids, tacrolimus, infliximab, azathioprine, calcineurin inhibitors, *etc*.) can also induce lymphoproliferative diseases [3, 5, 6]. A large range of lesions, from lymphoid hyperplasia to atypical lymphoproliferative disorders and malignant lymphomas, can be considered as iatrogenic disorders [1].

The lymph nodes, spleen and/or bone marrow can be affected and EBV infection can be involved. Post-transplant lymphoproliferative disease is a distinct lesion that is described below in the sub-chapter about transplantation, together with the EBV-related pathomechanism of its development [2].

CHAPTER 4

Iatrogenic Pathology of the Cardiovascular System

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Abstract: This chapter includes a synthesis of data regarding cardiovascular-related lesions induced by medical drugs or radiotherapy, and also relates to the specific injuries that can be caused by diagnostic and/or therapeutic interventions. The effects of chemotherapeutics and non-chemotherapeutic drugs on the myocardium are analyzed in detail, with a focus on anthracycline-induced cardiovascular effects in children. Some of the disorders are illustrated using representative pictures taken during autopsies. Although a common technique, insertion of prosthetic grafts can lead to complications, such as thrombosis, aberrant neointimal hyperplasia or dehiscence. Percutaneous vascular intervention complications can be related to the catheter or to the intervention itself. The differences between in-stent restenosis and postoperative thrombosis are also presented. The final part of this chapter is dedicated to open heart surgical intervention complications.

Keywords: Adverse drug reaction, Anthracyclines, Arrhythmia, Cardiovascular, Hypersensitive cardiomyopathy, Hypovolemia, Myocarditis, Neointimal hyperplasia, Open heart surgery, Percutaneous intervention, Prosthetic graft, Stenosis, Stent, Torsade de pointes, Vasculitis.

INTRODUCTION

Cardiovascular-related iatrogenic lesions can be induced by medical drugs (ADRs), radiotherapy performed to treat mediastinal or lung tumors (see Chapter 2), or diagnostic and therapeutic procedures. The specific ADRs and iatrogenic consequences of diagnostic and therapeutic procedures are presented in this chapter.

DRUG-INDUCED LESIONS

Chemotherapeutic Drugs

Hypersensitive-mediated cardiomyopathy and toxic myocarditis are the most

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severe chronic complications of antineoplastic therapy, especially in patients treated with *anthracyclines* (Table **4-1**). A 10-fold higher risk of developing heart failure has been reported in doxorubicin users when compared to healthy patients [1]. Anthracyclines-induced mitochondrial DNA damage is more severe in patients below the age of four and above the age of 65 [1, 2]. Their combination with cardiolipins in the internal membranes of mitochondria leads to depletion of adenosine triphosphate (ATP) and decreased myocardial contractility. Then, mitochondrial edema produces necrosis of cardiomyocytes and subsequent myocarditis and myocardial sclerosis [1, 2]. It is a cumulative lifetime dose-dependent mechanism.

In children, an average dose of 300 mg anthracyclines/m^2 is considered to produce clinical heart failure within about seven years. In some cases, heart transplantation is required approximately nine years after cancer diagnosis. Long-term monitoring of cardiotoxicity (echocardiography at 3, 6, 12, 36, 60 and 84 months after completion of treatment), identification and normalization of ejection fraction, and treatment of heart failure can increase life expectancy in these patients. At the same time, drugs to treat anti-anthracycline cardiac-induced lesions, such as dexrazoxane, can be simultaneously prescribed in adult patients but are not yet approved for children. ACE inhibitors can also be used for myocardial protection. A decrease of the left ventricular ejection fraction of over 10% below the lower value is an indicator for cessation of anthracycline-based therapy. In children, severe heart failure emerges as a result of anthracycline-induced cardiomyopathy, and cardiac transplantation offers a 50% chance of 10-year survival. This is the only therapeutic option in such cases [1].

Alkylating drugs, such as cyclophosphamide, can induce endothelial lesions and subsequent intramural hematomas and edema, but myocarditis and pericarditis have also been reported within two weeks of drug administration (Table **4-1**). However, in most cases, only transient arrhythmia presents [1].

Table 4-1. Cardiovascular-related ADRs induced by antineoplastic drugs. Data from references [1 - 7].

Type of ADR	Drugs
Angina	Anthracyclines, cyclophosphamide, 5-fluorouracil (5-FU)
Arrhythmia	Cyclophosphamide, anthracyclines (ventricular/supraventricular arrhythmia), 5-FU, lithium
Tachycardia	Anthracyclines (sinus tachycardia)
Torsade de pointes (polymorphic ventricular tachycardia) – QT prolongation or long QT syndrome	Anthracyclines

(Table 4-1) contd.....

Type of ADR	Drugs
Alterative myocarditis/ Myocardial fibrosis – toxic effect	Anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone), 5-FU, cyclophosphamide, isophosphamide
Cardiomyopathy	Lithium, anthracyclines (congestive cardiomyopathy and left ventricular hypertrophy)
Pericarditis/endocarditis	Anthracyclines, cyclophosphamide
Vasculitis/thrombosis	Cyclophosphamide, vaccines

Other chemotherapeutics known to induce cardiovascular disorders are *5-F--based agents* that can cause contraction of the coronary vessels with subsequent myocardial ischemia and arrhythmias [1]. Intravenous administration of 5-FU induces more severe cardiotoxicity as compared to oral fluoropyrimidine, such as capecitabine [4, 5]. However, even in cases of oral administration of capecitabine combined with oxaliplatin (XELOX or CAPOX regimens), long-term use at high doses induces cardiotoxicity in 1-18% of cases [5 - 7]. Angina is the most common consequence, but myocardial infarction and lethal myocardial fibrosis (Fig. **4-1**) occur in 11% of patients with capecitabine-induced cardiotoxicity [5 - 7].

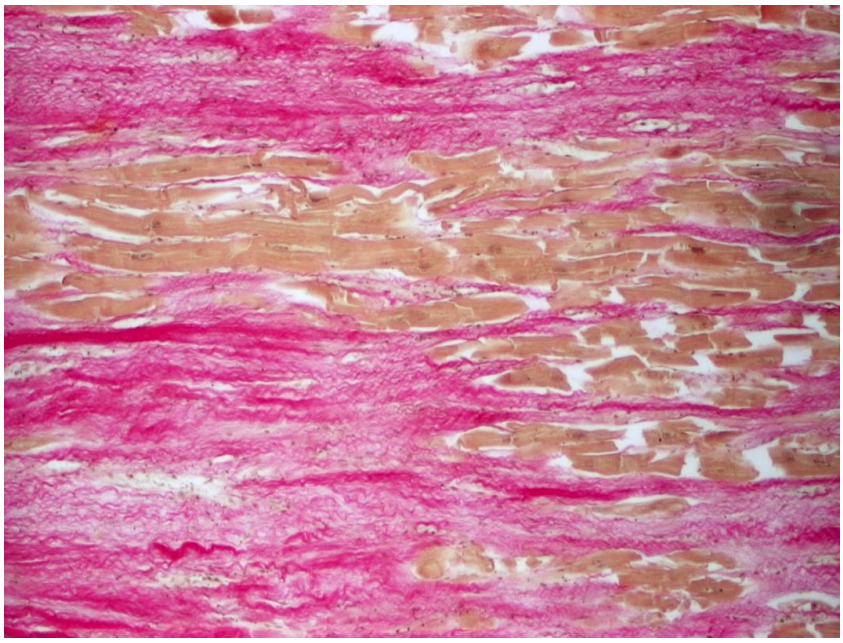

Fig. (4-1). Chemotherapy-induced lethal cardiotoxicity. The 36-year-old female received capecitabine and oxaliplatin, and subsequently developed diffuse myocardial fibrosis, emphasized in red with Van Gieson's stain. Ob. 4x.

CHAPTER 5

Iatrogenic Pathology of the Lungs and Airways

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Abstract: This chapter includes a synthesis of data regarding the lesions of the lungs and airways that can be induced by medical drugs or diagnostic and/or therapeutic interventions. Drug-induced lesions are difficult to identify and mainly relate to laryngeal or pulmonary edema, hypersensitivity pneumonitis and diffuse alveolar damage with hyaline membranes. In patients taking anticoagulants, the occurrence of spontaneous hemothorax or aberrant thromboembolism should also be taken into account. Diagnostic procedures that involve the airways are sometimes, though rarely, followed by complications that include post intubation croup, ulcerations or granulomas, but infrequent iatrogenic tracheal rupture and injuries to cranial nerves are also reported. Mechanical ventilation and hyperbaric oxygen therapy can be followed by pulmonary edema, interstitial emphysema or pneumothorax. In preterm babies, Wilson-Mikity syndrome and intraventricular brain hemorrhage can occur following oxygen therapy. All of these data are examined in detail in this chapter.

Keywords: Adverse drug reaction, Airways, Anaphylaxis, Aspiration, Croup, edema, Embolism, Hemothorax, Hyaline membranes, Hyperpigmentation, Intra-alveolar hemorrhage, Lung, Pneumonia, Pneumothorax, Respiratory distress syndrome, Wilson-Mikity syndrome.

DRUG-INDUCED LESIONS

The ADRs of the lungs and airways are caused by enzymatic deficiencies and can be induced through three basic mechanisms [1]:

- Immune hypersensitivity reactions – can cause anaphylaxis, bronchial asthma and eosinophilic pneumonia, and can be cured with steroids.
- Direct toxicity – drugs that are metabolized in the lungs can induce alveolocapillary damage. These dose-dependent injuries cannot be resolved using steroids.
- Idiosyncrasy – individual susceptibility that is not dose-dependent. This can start as a noncardiogenic pulmonary edema that can be handled with steroids.

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Up until the 1960s, about 20 drugs were reported to affect the lungs and bronchi [2]. Nowadays, it is known that more than 400 drugs can cause pulmonary disorders and 3-5% of all drugs present pulmonary toxicity [3]. Moreover, 0.03% of all in-hospital deaths seem to be caused by drug-induced pulmonary lesions [2].

The most common ADRs of the lungs and airways (Table **5-1**) are allergies and serum disease that can be associated with ***acute laryngeal edema***. Eighty-four drugs are known to induce anaphylaxis, leading to anaphylactic shock (76.6%), severe systemic reactions (10.5%), acute laryngeal edema (9%), severe bronchospasm (2.1%) and death (1.8%) [4].

Acute pulmonary edema can be a consequence of inhalation of pure oxygen, administration of nitrofurantoin or intravenous perfusions with a high volume of liquid. It is worth mentioning that concomitant administration of steroids causes salt and water retention [5].

The antiarrhythmic amiodarone is considered the most common drug to induce dose-dependent direct toxicity in the lungs (Table **5-1**). Approximately 5-6% of patients treated with amiodarone present lung disorders, from mild ***pneumonia*** to severe lesions, such as ***intra-alveolar hemorrhages*** and ***diffuse alveolar damage with hyaline membranes*** [1, 3, 7].

Other drugs known to induce pulmonary disorders are antibacterial agents, such as nitrofurantoin, and immunosuppressive drugs, such as sirolimus, *etc*. (Table **5-1**) [2, 8].

Drug-induced pulmonary injuries are more frequently found in patients of extreme ages, due to low renal filtration [7]. Some drugs, such as nitrofurantoin, especially affect women, though the cause is yet unknown [3].

Genetic factors influence the reactions of the body. In patients treated with gefitinib, an anti-EGFR agent that is used in patients with non-small cell lung cancer, ***interstitial pneumonia*** is a rare side effect in Europe but quite common in Japan. Similar divergence is reported for bortezomib (used in multiple myeloma and lymphomas) and tacrolimus (an immunosuppressive drug used in bone transplant recipients) – their pulmonary toxicity being more common in Japanese and African-American populations. At the same time, methotrexate-related pulmonary toxicity is more common in patients testing positive for HLA-B40 [3].

Because idiosyncratic reactions are more common than we know, drug-induced lung injury is usually a diagnosis of exclusion. To confirm one's suspicion, nonspecific clinical symptoms (dry cough, subfebrility, dyspnea, wheezing, hypoxemia, chest pain, fatigue, allergic reactions, rash, arthralgia, *etc*.) should be

correlated with the presence of alveolar/interstitial/mixed inflammatory foci with asymmetrical distribution, subpleural masses, pleural thickening and effusion, altered lung function (decrease of carbon monoxide diffusing capacity), hematological disturbances (increased CD8+ lymphocytes, neutrophils and eosinophils) and occurrence of foamy macrophages and eosinophils in the bronchoalveolar lavage fluid [2]. The diagnosis of drug hypersensitivity is based on skin tests (72.9% of cases) correlated with laboratory examinations [4].

Table 5-1. ADRs of the lungs and airways according to specific drugs. Data from references [1 - 20].

ADR type	**Drugs**
Cough, hiccup, laryngospasm, bronchospasm	Thiopental, inhalational anesthetics (desflurane), NSAIDs, beta blockers, mitomycin C (antitumor antibiotic)
Anaphylaxis	Antibiotics (penicillin, cephalosporin, quinolone, *etc*.), muscle relaxants, latex, anesthetic NSAIDs, acetaminophen, iodinated or MRI contrast media, immunotherapy, vaccines
Airway infections	Topiramate (anticonvulsant)
Bronchial dilation	Halothane
Bronchiolitis obliterans	Cyclophosphamide, methotrexate, penicillin
Hyperpigmentation of bronchial mucosa	Busulfan
Iatrogenic bronchial asthma	Aspirin, NSAIDs (indomethacin)
Alveolar hypoventilation	Narcotics, aminoglycosides, corticosteroids
Acute pulmonary edema	Oral corticosteroids and perfusions, amiodarone, nitrofurantoin, narcotics, tocolytics, depolarizing myorelaxants (succinylcholine) used in newborns and infants, biological monoclonal antibodies
Intra-alveolar hemorrhage	Aspirin, anticoagulants, amiodarone, sirolimus (rapamycin)
Eosinophilic (Löffler's) pneumonia	Cytotoxic drugs (bleomycin), antibiotics (penicillin), sulfonamides, nitrofurantoin, methotrexate, phenytoin (anticonvulsant), para-aminosalicylic acid (mesalazine)
Acute fibrinous pneumonia	Amiodarone, aciclovir, decitabine, proton pump inhibitors (PPIs)
Interstitial pneumonia/ lung fibrosis	Cytotoxic drugs (busulfan, bleomycin, methotrexate, procarbazine, cyclophosphamide, chlorambucil, azathioprine), nitrofurantoin, amiodarone, carbamazepine, gleevec, mesalazine, bleomycin, pingyangmycin (bleomycin derivative with sclerosant effect), nitrogen mustard (alkylating drug)
Lipoid pneumonia	Amiodarone or chronic aspiration of nasal drops
Perivascular and peribronchial fibrosis	LSD (lysergic acid diethylamide) – analogs (dose-dependent ADR)
Secondary tuberculosis	Corticosteroids, cytotoxic drugs

CHAPTER 6

Iatrogenic Pathology of Gastrointestinal Tract

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Abstract: This chapter includes a synthesis of data regarding iatrogenic injuries of the gastrointestinal tract. In the first section, medical drug-induced lesions are analyzed, while the following sections refer to the diagnostic and/or therapeutic interventions that involve the gastrointestinal segments. ADRs come in a wide spectrum of manifestations, from mucosal inflammation to severe lesions, such as Stevens-Johnson syndrome. The most common agents involved in severe reactions are non-steroidal anti-inflammatory drugs (NSAIDs). Proton pump inhibitors (PPIs) are responsible for the occurrence of cystic polyposis of the stomach. Intestinal iatrogenic disorders primarily involve enterocolitis, but strange complications, such as bezoar formation or intestinal rupture, are also reported. Complications relating to endoscopic examinations, laparotomy and laparoscopy are also presented in detail.

Keywords: Adverse drug reaction, Aspiration, Bezoar, Cystic polyposis, Endoscopy, Enterocolitis, Gingival hyperplasia, Hemorrhage, Laparoscopy, Laparotomy, Malabsorption, Polyp, Proton pump inhibitors, Stevens-Johnson syndrome, Teeth discoloration.

DRUG-INDUCED LESIONS

ADRs of the GI tract (Table **6-1**) can be induced *via* the following mechanisms: dose-dependent direct toxicity (*e.g.,* PPIs), immune hypersensitivity reactions, idiosyncrasy and mixed mechanisms (*e.g.,* NSAIDs) [1].

Lesions of the Oral Cavity, Pharynx And Esophagus

- ***Mucosal Inflammation***

Antibiotics, conventional chemotherapeutics, immunosuppressive drugs and targeted cancer therapeutics (*e.g.,* mTOR and tyrosine kinase inhibitors, antiangiogenic drugs) can cause stomatitis, pharyngitis, esophagitis and angina. These types of mucositis can be ulcerative, mycotic (*e.g.,* candidiasis) or

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gangrenous [1 - 3].

- ***Other Lesions of the Oral Mucosa***

These are presented in detail in Table **6-1**. For example, *gingival hyperplasia* can be induced by anticonvulsants or contraceptives. In psychiatric patients receiving antipsychotics, *Stevens-Johnson syndrome* has been reported; skin lesions (described in Chapter 13) are associated with edema and ulcers of the oral and ocular mucosa [4].

Tetracyclines can produce *discoloration of the teeth* and can also, during the childhood period, induce hyperplasia or deformities of the teeth enamel. Although iron supplementation confers protection against enamel demineralization, it can also induce black teeth discoloration in children, especially in hypomineralized and decalcified areas. Because staining intensity is directly correlated with the supplements' contact with teeth, and the duration of that contact, simultaneous consumption with liquids or dripping directly to the posterior parts of the mouth is suggested [1, 5].

- ***Other Lesions of the Esophagus***

Doxycycline may induce hemolysis and epithelial injury with subsequent esophageal *erosion*. Polymedication can result in *dysphagia*. Chemotherapeutics can produce taste disorders (*dysgeusia/ageusia*) and esophageal *strictures* [3, 6 - 9].

Table 6-1. ADRs of the salivary glands, oral cavity and esophagus. Data from references [1 - 9].

ADR type	Drugs
Acute sialorrhea/hypersalivation	Ketamine (intravenous anesthetic drug)
Hyposalivation/xerostomia	Antihistaminic drugs, atropine, belladonna neuroleptics (promethazine)
Dysphagia, dysgeusia	Chemotherapeutics (vismodegib)
Parotitis	Morphine
Increased appetite	Corticosteroids
Yellow, brown or black teeth (teeth discoloration)	Tetracyclines, iron supplements, augmentin (amoxicillin with clavulanate)
Erythema multiforme of the mouth	Aspirin, barbiturates, bromide, hydantoin, iodine, antibiotics (penicillin, streptomycin), sulfonamides, thiouracil
Mouth ulcerations	Antipsychotics (carbamazepine, phenytoin, clozapine), mTOR inhibitors, chemotherapeutics

(Table 6-1) contd.....

ADR type	Drugs
Gingival hyperplasia	Antiepileptic drugs (hydantoin), contraceptive pills, cyclosporine, atropine, belladonna
Esophageal erosions	Antibiotics (*e.g.,* doxycycline), NSAIDs, potassium chloride, chemotherapeutics (*e.g.,* carboplatin and paclitaxel)
Necrotizing inflammations	Cytotoxic drugs (*e.g.,* cyclophosphamide), immunosuppressives
Esophageal strictures	Chemotherapeutics (vinblastine, doxorubicin, 5-FU, rituximab, methotrexate, *etc*.)
Mycotic infections	Antibiotics, immunosuppressive drugs
Mucosal hyperpigmentation	Cyclophosphamide, doxorubicin, busulfan, augmentin

Gastric Disorders

- ***Acute/Chronic Gastritis with Associated Erosions or Peptic Ulcers***

Gastric mucosal lesions (Table **6-2**) can be induced by several drugs, including antibiotics, sulfonamides, corticosteroids, chemotherapeutics, rauwolfia-based drugs, *etc.* [10, 11]. Ulcerations are present in about 20% of long-term users of NSAIDs [12]. Aspirin is the cause of 50% of gastric erosion. The pathomechanism involves direct injuries to the gastric mucosa-defending barriers. This is followed by increasing ion permeability and back diffusion of hydrogen ions across the gastric mucosa, with further mastocyte degranulation and histamine release. This, in turn, leads to chloride acid hypersecretion and subsequent mucosal erosions, superficial necroses and bleeding [13]. Acute gastritis is common in patients hospitalized in ICUs (Fig. **6-1**).

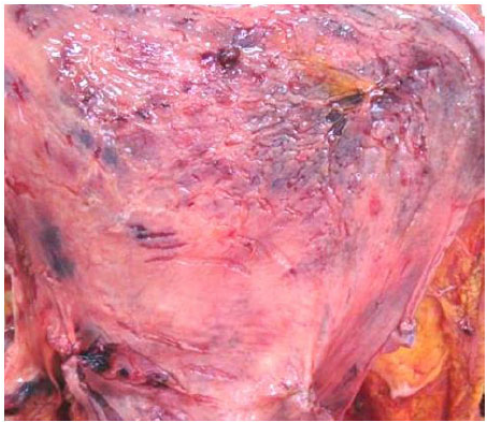

Fig. (6-1). Acute gastritis with erosions.

CHAPTER 7

Iatrogenic Pathology of the Peritoneum and Retroperitoneum

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Abstract: This chapter presents a synthesis of data regarding the iatrogenic injuries of the peritoneum and retroperitoneum. Similar to the previous chapters, medical drug-induced lesions and the consequences of diagnostic and/or therapeutic interventions are presented in detail. Iatrogenic retroperitoneal fibrosis can emerge following radiotherapy or as a consequence of long-term use of drugs such as beta blockers or antiepileptic substances. Pneumoperitoneum is usually a postoperative transient lesion, but it can also be a severe consequence of barotrauma or mechanical ventilation. The causes and consequences of iatrogenic peritonitis and ascites are also analyzed.

Keywords: Adverse drug reaction, Ascites, Barotrauma, Beta blockers, Hematoma, Hemoperitoneum, Hydralazine, Iatrogenic, Peritoneum, Peritonitis, Pneumoperitoneum, Retroperitoneal emphysema, Retroperitoneal fibrosis, Retroperitoneum.

DRUG-INDUCED LESIONS

Hemoperitoneum can occur in patients taking anticoagulants as a spontaneous lesion or secondary to drug-induced spleen rupture [1, 2].

Retroperitoneal Fibrosis is, in 85% of cases, an idiopathic primary lesion known as Ormond's disease. Secondary fibrosis can be induced by drugs (Table **7-1**), radiotherapy performed for abdominal tumors or surgical intervention. It is accompanied by a high risk of developing progressive renal failure; uretero-hydronephrosis is associated in 63% of patients. The treatment comprises steroids and immunosuppressive drugs, but azathioprine, methotrexate and cyclosporine are sometimes necessary [3, 4].

Sclerosing Peritonitis involves extensive fibrosis of the wall of the small intestine and mesenterium followed by intestinal stenosis or obstruction. The

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idiopathic type was first reported by Owtschinnikow in 1907, whereas the secondary type was only identified in 1978, occurring after prolonged peritoneal dialysis. It can also be induced by drugs (*e.g.,* beta blockers, antiepileptics) or as a complication of intestinal transplantation [4 - 6].

Table 7-1. Drug-related peritoneal lesions. Data from references [1 - 4].

LESION	Drugs
Hemorrhages	Anticoagulants, antiplatelet drugs, cytotoxic drugs
Fibrosis	Hydralazine, beta blockers (*e.g.,* propranolol), methyldopa, LSD analogs (dose-dependent effect), nicotinic acid, procaine-polyvinylpyrrolidone, ergotamine, belladonna, analgesics, methysergide, antiepileptic drugs

IATROGENIC LESIONS DURING DIAGNOSTIC AND THERAPEUTIC PROCEDURES

Pneumoperitoneum and Retroperitoneal Emphysema

Transient ***pneumoperitoneum*** without associated bowel perforations occurs in 60-80% of abdominal surgical interventions and is usually without clinical impact. About 500-1000 ml of air is accumulated in the peritoneal cavity and is spontaneously absorbed within 10 days. In most cases, no clinical consequences are reported, but secondary fibrotic adherences or compression of the abdominal organs can occur. Besides abdominal surgery, pneumoperitoneum can also be a consequence of gynecological surgery or GI tract endoscopy as a result of bowel perforation [4, 7, 8]. Endoscopic resection of gastric tumors and endosonography-guided biliary drainage are also reported to induce pneumoperitoneum [9, 10].

Tension Pneumoperitoneum can be a consequence of barotrauma. It produces progressive compression of the abdominal organs and large vessels (abdominal aorta, inferior cava vein) and can induce abdominal compartment syndrome [4, 11]. Tension pneumoperitoneum can also emerge after laparoscopic interventions and can lead to subcutaneous emphysema, tension pneumothorax and pneumomediastinum [12]. In 4% of children undergoing pneumatic reduction of ileal intussusception, tension pneumoperitoneum emerged during air enema reduction. Needle decompression and subsequent laparotomy with bowel resection is the treatment of choice [13].

Retroperitoneal Emphysema can be a consequence of mechanical ventilation. The pathomechanism involves high pressure-induced interstitial emphysema of the lung and mediastinal tissues, with subsequent propagation of the air through the retroperitoneum and peritoneal cavity. The air is either totally absorbed or its

accumulation leads to peritoneal adherences and/or emphysema of the abdominal tissues [4, 7].

Retroperitoneal Hematoma and Hemoperitoneum

In patients undergoing cardiac angiography or angioplasty, retroperitoneal hematoma can occur during catheter advancement as a result of dissection and/or rupture of the abdominal aorta [14]. In our experience, this lesion has been identified at autopsy in only one case. This was the case of a 62-year-old male with severe atherosclerosis who presented a periprocedural intramural hematoma as a result of rupture of an atherosclerotic plaque of the abdominal aorta. Within a few hours of intervention, rupture of the hematoma led to fatal retroperitoneal hematoma and hemorrhagic shock.

Retroperitoneal bleeding can also occur during open or laparoscopic abdominal, urological or gynecological surgery as a result of rupture of the major vessels [15, 16]. During spinal surgery, injuries of the lumbar artery can lead to formation of a pseudoaneurysm and delayed retroperitoneal hematoma [17]. Moreover, because the aortic bifurcation is near to the anterior surface of the L4-L5 disc, lumbar discectomy can lead to dilacerations of the aorta and subsequent retroperitoneal hemorrhage [18].

In patients with polycystic kidney, hemodialysis can induce rupture of the cystic structures and retroperitoneal hemorrhage [19]. In children, retroperitoneal hemorrhage can occur after cardiopulmonary resuscitation [20].

Postoperative Peritonitis

Iatrogenic peritonitis can be an infective or non-infective, acute or chronic, localized or diffuse, exudative or granulomatous inflammation.

- ***Diffuse Purulent Peritonitis***

  This is an infective inflammation that can occur after abdominal surgery, including laparoscopy, or as a complication of hemodialysis [21]. Incidental rupture of the intestine can occur in pediatric surgery, but can be intraoperatively handled (Fig. **7-1**).

- ***Bile Peritonitis***

  This is a non-infective peritonitis caused by bile extravasation into the abdominal cavity. The bile can be released following rupture of the bile ducts (during cholecystectomy, endoscopic retrograde cholangiopancreatography or

CHAPTER 8

Iatrogenic Pathology of the Liver, Gallbladder and Pancreas

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Abstract: This chapter presents a synthesis of data regarding iatrogenic injuries of the liver, gallbladder and pancreas. For each of these organs, medical drug-induced lesions are presented. The second part of the chapter includes the consequences of diagnostic and/or therapeutic interventions for the above-mentioned organs. The liver is the second most common organ involved in drug effects, following the skin. Its destruction can be an indication for transplantation. The hepatic disorders include metabolic disturbances, cholestasis, hepatitis, cirrhosis and risk of malignancy. The biliary channels can be injured during open surgical interventions or laparoscopic cholecystectomy, leading to fistulae, peritonitis, bilirrhagia and even death. Endoscopic retrograde cholangiopancreatography (ERCP) can be associated with local complications, such as pancreatitis and cholangitis, but pneumothorax, pneumomediastinum and pneumoretroperitoneum are also encountered in rare cases.

Keywords: Adverse drug reaction, Allergy, Bilirrhagia, Cholangiopancreatography, Cholecystectomy, Cholestasis, Cirrhosis, Gallbladder, Hematoma, Hepatitis, Hepatocellular carcinoma, Hepatoportal sclerosis, Iatrogenic, Liver, Pancreas, Pancreatitis, Peritonitis.

DRUG-INDUCED LESIONS

Besides the skin, the liver is the most common organ that presents drug-induced lesions. Moreover, liver injuries are the most common reason for drug withdrawal from the pharmaceutical market (*e.g.,* troglitazone, bromfenac) and the leading cause for liver transplantation [1]. The worldwide incidence of drug-induced liver injuries is between two and 24 cases per 100,000 people per year [1]. These injuries can include metabolic disorders, acute cholestasis with reversible focal necroses, granulomatous/fulminant hepatitis, chronic liver injury (toxic hepatitis, steatosis, cirrhosis, hepatoportal sclerosis), high serum levels of transaminases,

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hepatomegaly and neoplastic lesions (hepatocellular carcinoma, cholangiocarcinoma, angiosarcoma) [2]. In our practice, we have encountered a few cases in which liver transplantation was necessary due to severe liver failure that occurred as a result of consumption of weight-loss pills, in young females, or anabolic substances, in males.

Mechanisms of ADRs

Hepatopancreatic drug-related lesions can be induced through dose-dependent toxicity or through allergic or idiosyncratic mechanisms (dose-independent ADR) [1].

Dose-Dependent Hepatopancreatic Toxicity

The most common dose-dependent *hepatotoxic drugs* are aspirin, salicylates, chemotherapeutics, steroids, methyltestosterone and estrogen (Table **8-1**). Chemotherapeutics, such as capecitabine and oxaliplatin, can induce steatohepatitis (Fig. **8-1**), sinusoidal obstruction syndrome, liver fibrosis and liver failure [3 - 5]. Long-term consumption of androgenic steroids-based contraceptive pills is a risk factor for hepatocellular adenoma (with an annual incidence of between three and four cases per 100,000 females) and even hepatocellular carcinoma [6].

Drug-related *pancreatitis* is reported by the WHO to be induced by more than 500 drugs, but direct toxic effect has been proven for 31 drugs only [7]. These include chemotherapeutics (Fig. **8-1**), paracetamol, steroids, procainamide, *etc*. [8]. Simultaneous administration of capecitabine and oxaliplatin can also induce hypertriglyceridemia [3 - 5].

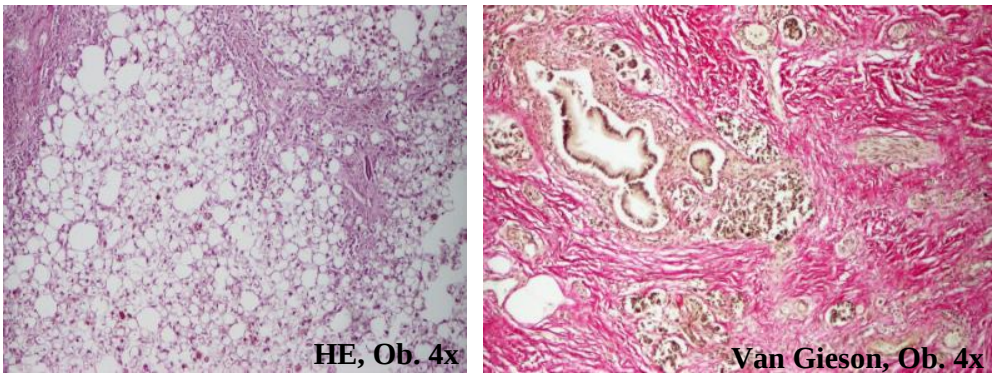

Fig. (8-1). Chemotherapy-associated hepato-pancreatic lesions. Steatohepatitis (left) and chronic pancreatitis (right) induced by capecitabine and oxaliplatin.

Allergic and Idiosyncratic Drug Reactions

These mechanisms are more frequently involved in drug-induced hepatic disorders than dose-dependent lesions. Hepatopancreatic lesions arise within several weeks of the completion of treatment. Systemic reactions, such as fever, rash, arthralgia and eosinophilia, can be associated [1, 2, 9].

Hepatopancreatic Lesions Induced Through Mixed Mechanisms

Halothane-related hepatitis is produced through direct toxicity combined with hypersensitivity and genetic susceptibility [10]. The associated yellowish liver presents large necrotic areas under the microscope (Fig. **8-2**).

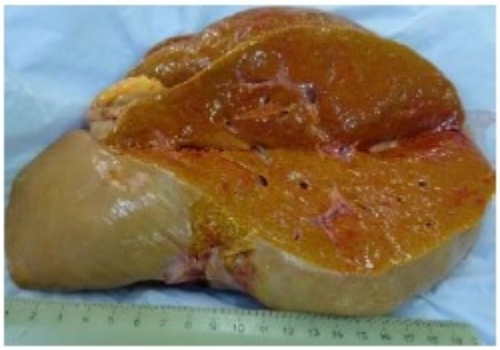

Fig. (8-2). Halothane-induced hepatitis with necrosis.

Drug-Induced Diabetes and Hyperglycemia can be the result of direct toxic effect or alterations in insulin secretion and sensitivity. They can be caused by several drugs, including steroids, nicotinic acid, statins, thiazide diuretics, fluoroquinolones, phenytoin, valproic acid, pentamidine, growth hormones, somatostatin analogs, beta blockers, calcium channel blockers and inhibitors of the renin-angiotensin system (Table **8-1**) [11]. In pediatric departments, medication-induced diabetes is especially reported in children with leukemia treated with L-asparaginase and glucocorticoids [12].

Table 8-1. Drug-induced hepatopancreatic injuries. Data from references [1 - 20].

Lesion	Drugs
High level of serum transaminases, jaundice	Augmentin (amoxicillin with clavulanic), neuroleptic/antidepressant drugs (chlorpromazine, lithium, tiotixen, triflupromazine, tranylcypromine)

CHAPTER 9

Iatrogenic Pathology of the Kidney and Urinary System

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Abstract: This chapter presents a synthesis of data regarding acute and chronic drug-related lesions of the kidneys and urinary tract, as well as the urologic injuries that can result from diagnostic and/or therapeutic interventions. Reversible or irreversible renal injuries can be caused by prerenal, intrarenal or postrenal damage. Identification of the pathomechanism is mandatory for proper treatment of the side effects. Those drugs that are excreted through the kidneys can induce ischemic or obstructive lesions and can predispose the patient to stone formation. Analgesic nephropathy is a particular type of nephritis that can be reversible after drug cessation. Glomerulonephritis can be caused by several drugs, including vaccines, anti-inflammatory agents and beta blockers. Regarding surgical interventions, upper urinary tract deterioration can occur following direct injuries or as a consequence of iatrogenic lumbosacral spinal cord lesions. Complications relating to peritoneal dialysis are also presented in detail.

Keywords: Adverse drug reaction, Analgesic nephropathy, Azotemia, Cystitis, dialysis, Glomerulopathy, Hemolysis, Iatrogenic, Kidney, Lithiasis, Nephritis, Papillary necrosis, Percutaneous intervention, Urinary tract, Vasculitis.

DRUG-INDUCED LESIONS

Drug-induced renal injuries can be reversible or irreversible, acute or chronic processes (Table **9-1** and Table **9-2**). The mechanism involves damage at one of the following three levels: prerenal (volume depletion and electrolytes disturbances), intrarenal (direct toxicity, pro-inflammatory effect or drug-induced obstructive or ischemic lesions) and postrenal (promoters of stone formation) [1].

Acute kidney injuries are identified based on albuminuria and elevated levels of serum creatinine and blood urea nitrogen. Other recently proposed serum biomarkers are kidney injury molecule-1, neutrophil gelatinase-associated lipocalin and N-acetyl-β-d-glucosaminidase [2].

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Prerenal Azotemia can be caused by mannitol, diuretics and antihypertensive drugs that act as vasodilators and induce hypovolemia [1].

Intrarenal Injuries primarily refer to tubular lesions, but secondary parenchymatous damage is associated. Glomerulonephritis and interstitial nephritis are generated through immune complex hypersensitivity (type III) reaction. Acute interstitial nephritis can be a dose-dependent lesion in long-term users of proton pump inhibitors (PPIs). Vascular lesions can also occur. Due to the inhibition of prostaglandin synthesis, NSAIDs produce impaired perfusion with subsequent acute allergic interstitial nephritis and/or acute toxic tubular necrosis [1, 3].

Postrenal Injuries are primarily dose-dependent lesions and include urethral obstruction and risk of stone formation [4].

Analgesic Nephropathy

This is a particular type of *drug-induced chronic nondestructive interstitial nephritis* that is characterized by interstitial fibrosis and tubular atrophy. In severe forms, papillary necrosis can occur (Fig. **9-1**). Sclerosis of the medullary capillaries and fibrosis of the mucosa lining calices, pelvis and ureters can be associated [5, 6]. Chronic renal failure is reported in one third of patients. This type of nephritis is caused by the chronic use of analgesics (phenacetin, acetaminophen, saridon, *etc*.) or NSAIDs [4, 7].

The treatment involves drug cessation. Due to progressive renal failure, the clinical symptoms are polyuria, polydipsia and hypertension. This lesion predisposes the patient to urothelial carcinoma, the incidence of which is 13 times higher than in the control group. The risk of urothelial carcinoma of the renal pelvis, furthermore, is 75 times higher than in the control group [4, 7].

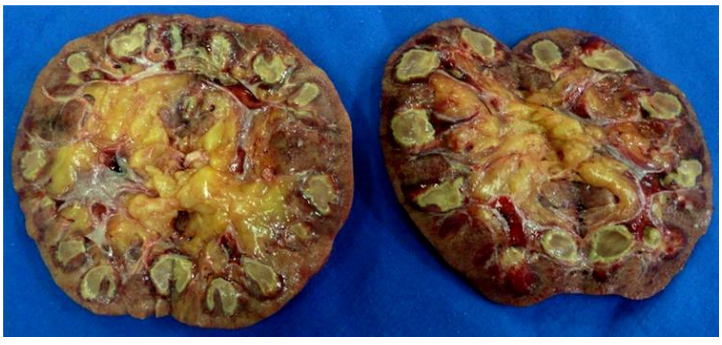

Fig. (9-1). Bilateral papillary necrosis in a patient with chronic interstitial nephritis.

Other Drug-Induced Renal Injuries

These lesions are presented in Table **9-1** and Table **9-2**. The most common specific drug-related effects are the following [4, 8 - 10]:

Contrast Agents (*e.g.,* iodine-based substances) can produce tubular lesions which induce acute/chronic renal failure, acute/chronic nephrotic syndrome, fluid and electrolyte imbalance, acid-base disorders, *etc*.

Antibiotics (*e.g.,* gentamicin, tobramycin, cephalosporin) present a dose-dependent tubular toxicity. The tetracyclines present an anabolic effect and can induce tubulonephrosis. Amphotericin produces vasoconstriction of the small arteries and arterioles.

Diethylenetriamine (DETA) is an organic compound used in patients with lead or other metal intoxications, which can induce tubulonecrosis of the proximal tubes.

Cyclosporine and Rapamycin induce functional disorders due to their inhibition of calcineurin.

Serum Immunization and Vaccination can cause an immune-mediated crescentic or membranous glomerulonephritis.

Lithium Nephropathy can occur in patients with mood or bipolar disorders, or other psychiatric illnesses, who take lithium compounds for more than one or two years. It is characterized by a wide range of spectrum injuries, from a minimal decrease of the glomerular filtration rate to tubulointerstitial nephropathy and renal failure. The consequences are more severe in young females.

Table 9-1. Drug-induced tubular lesions and functional disorders. Data from references [1 - 10].

ADR type	Drugs
Tubular toxicity	Cisplatin, nedaplatin, amphotericin B, tacrolimus, carbamazepine, aminoglycosides, quinolones, ifosfamide, radiocontrast substances, mannitol, dextran, mithramycin, pentamidine, methoxyflurane, tetracycline, cephaloridine, streptozotocin, foscarnet, zoledronate, cidofovir, adefovir, tenofovir, hydroxyethyl starch, intravenous gamma globulin
Acute tubulonecrosis	NSAIDs, aminoglycosides, amphotericin, cyclosporine, sulfonamides, cephalosporins, tetracycline, rifampicin, cytotoxic drugs (cisplatin, methotrexate, mithramycin, nitrosourea)
Rhabdomyolysis (obstructive tubulopathy)	Lovastatin, ethanol, barbiturates, diazepam, codeine

CHAPTER 10

Iatrogenic Pathology of the Female Genital System and Breast

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Abstract: The female genital system and breast can be injured by drugs or during diagnostic and/or therapeutic interventions. Drug-induced lesions of the female genitalia primarily involve contact dermatitis and fixed drug eruptions. Galactorrhea can be caused by several drugs, including neuroleptics and antihypertensive agents. In females with breast cancer, tamoxifen can induce endometrial hyperplasia and transformation into carcinoma. Diagnostic and therapeutic procedures rarely lead to severe complications, but such complications are specific and require knowledge for clinicians. The final section of this chapter is reserved for specific lesions related to pregnancy and the effects of the intrauterine environment on newborns.

Keywords: Adverse drug reaction, Allergy, Breast, Dermatitis, Endocervical hyperplasia, Endometrial atrophy, Endometrial hyperplasia, Female genitalia, Fixed drug eruption, Galactorrhea, Genital system, Iatrogenic, Newborn, Pregnancy, Urticaria.

DRUG-INDUCED LESIONS

Lesions of the Female Genitalia

These lesions are local injuries produced by gels, creams and topical antiseptics, as well as lesions secondary to the systemic administration of drugs.

Iatrogenic Contact Dermatitis And/Or Urticaria is the most common local injury of the female genitalia and is produced through type IV hypersensitivity reaction. It can be induced by topical agents, a patient's latex allergy, methylisothiazolinone, *etc.* [1].

Genital Fixed Drug Eruptions represent recurrent, well-defined lesions appearing on the external genital organs each time the responsible drug is taken.

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They may be related to oral or systemic administration of several drugs (Table **10-1**). Genital ulcers can be associated [1 - 5].

Gonadotropin-Releasing Hormone (GnRH) Agonists are used to preoperatively shrink leiomyomas, to control bleeding and for patients with contraindications for myomectomy. These drugs induce several side effects, including the climacteric effect. To avoid these effects, other combinations are introduced in daily practice. Administration of combined oral contraceptives, progestins- or levonorgestrel-releasing intrauterine devices (IUDs) have proven to be appropriate for bleeding control but not for quick and significant fibroids shrinkage. A new selective progesterone receptor modulator is ulipristal acetate (UPA), which induces amenorrhea and seems to cause long-term shrinkage of leiomyomas [6].

Other female genitalia-related ADRs are presented in Chapter 18.

Table 10-1. Female genitalia-related ADRs. Data from references [1-6].

ADR type	Drugs
Genital fixed drug eruptions	Antifungals (ketoconazole), antiparasitic agents (metronidazole, miconazole) quinine, antibacterial sulfonamides, NSAIDs (ibuprofen), antimalarial drugs, antibiotics (amoxicillin), antihistamines, steroids, *etc*.
Genital ulcers	NSAIDs, antimalarials, ACE inhibitors, beta blockers, lithium, salicylates, corticosteroids, tyrosine kinase inhibitors (*e.g.,* sunitinib)
Hypermenorrhea	Neuroleptics/antidepressant drugs (reserpine)
Amenorrhea, low prolactin levels	Antiemetics, neuroleptics/tricyclic antidepressants (haloperidol, chlorpromazine, sulpiride), cytotoxic drugs (cyclophosphamide)
Time-dependent amenorrhea (more than three months of daily use)	Ulipristal acetate (UPA, a progesterone receptor modulator used to preoperatively shrink symptomatic leiomyomas)
Fungal infections (vulvovaginitis)	Immunosuppressive drugs, corticosteroids, antibiotics
Endocervical hyperplasia, endometrial atrophy, uterine hemorrhages, anovulatory infertility and virilization	Contraceptive pills, progesterone (gestagens)
Endometrial hyperplasia/adenocarcinoma, anovulatory infertility, increased risk of thrombosis and breast cancer	Estrogens, tamoxifen
Ovarian hyperstimulation syndrome, multiple gestation, ectopic pregnancy, adnexal torsion, hemoperitoneum	Gonadotropin

Lesions of the Breast

The most common drug-induced lesions of the breast are galactorrhea, lactation abnormalities and necroses (Table **10-2**).

Table 10-2. Drug-induced lesions of the breast. Data from references [1-6].

ADR type	Drugs
Galactorrhea	Neuroleptic drugs, contraceptive pills, antihypertensive agents, antiemetics
Lactation abnormalities	Antiemetics, antipsychotics, tricyclic antidepressants
Breast hemorrhagic necrosis	Anticoagulants
Breast tenderness	Gonadotropin

IATROGENIC LESIONS DURING DIAGNOSTIC AND THERAPEUTIC PROCEDURES

Non-Surgical or Minimally Invasive Procedures

Endoscopic Examinations can be followed, though rarely, by local hemorrhages and/or ascending infections [7].

Hysterosalpingography can be associated with contrast agent-related complications. Such substances can initiate an allergy or can induce granulomatous salpingitis or peritonitis [8].

Contraceptive IUDs can induce several complications, such as acute/chronic endometritis, cervicitis, vaginitis, tubo-ovarian abscess with subsequent ectopic pregnancy, pelvic actinomycosis, endometrial atrophy/fibrosis, endometrial carcinoma, *etc.* [7].

Curettage of the Intrauterine Cavity (after delivery, abortion or tumor removal) can be followed by infections (endomyometritis), Asherman's syndrome (trauma-related endometrial atrophy, hypo-/amenorrhea, sterility), *etc.* [9].

Uterine Artery Embolization is performed in patients with leiomyomas and can be complicated by Asherman's syndrome. It can also be followed by formation of intrauterine fibrous membranes; the outcome of hysteroscopic adhesiolysis is worse in females with Asherman's syndrome [9]. Other complications are infections, necrosis, ovarian insufficiency and premature menopause (amenorrhea, high follicle stimulating hormone [FSH] levels) [10].

CHAPTER 11

Iatrogenic Pathology of the Male Genital System

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Abstract: Similar to the female genital system, the male genitalia can be injured by drugs or during diagnostic and/or therapeutic interventions. The drug-induced lesions of the male genitalia that are analyzed in this chapter include contact dermatitis, fixed drug eruptions, scrotal blisters and other specific lesions, such as red scrotum syndrome and scrotum hemangioma. Iatrogenic functional disorders are also presented in detail. The final section of this chapter is dedicated to surgical-related lesions of the male genitalia.

Keywords: Adverse drug reaction, Allergy, Circumcision, Dermatitis, Fixed drug eruption, Genital system, Gynecomastia, Hemangioma, Hyperplasia, Iatrogenic, Male genitalia, Prostate, Red scrotum syndrome, Urticaria.

DRUG-INDUCED LESIONS

Lesions of the External Genitalia

Local Irritation or Contact Dermatitis may be the result of local application of topical agents, such as miconazole [1].

Genital Fixed Drug Eruptions with/without genital ulcerations or necroses may occur following oral or systemic administration of several drugs (Table **11-1**). For example, in a 55-year-old man, a scrotal erythematous patch with pruritus was reported a few days after receiving miconazole and sulpiride for buccal mycosis. Three months later, the patient self-medicated with miconazole gel and the lesion reoccurred accompanied by a penile rash. This disappeared after drug cessation [1 - 6].

Scrotal Blisters can be seen in patients with chemotherapy-related hand-foot syndrome. Tyrosine kinase inhibitors, such as sorafenib, can be involved in their occurrence [7].

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Red Scrotum Syndrome is characterized by a burning or itching painful erythema of the scrotum and can be a side effect of topical steroids. Under the microscope, erythematotelangiectatic rosacea-like lesions can be seen [8].

Vitiligo of the penis and scrotum has been reported in males using imiquimod 5% cream for HPV-related condylomata accuminata, Bowen's disease, warts or superficial carcinoma [9].

Scrotum Hemangioma can develop in patients receiving the multi-targeted tyrosine kinase receptor inhibitor sunitinib. This progressively increasing lesion occurs approximately 20 days after the third cycle of targeted therapy. Ulceration can be associated [10].

Isolated Genital Edema is an angioneurotic edema that can occur in patients taking ACE inhibitors or other drugs [11]. Iatrogenic scrotal edema is especially frequently reported in children as a result of perfusion-related hyperhydration (Fig. **11-1**) or in patients with poorly controlled diabetes following administration of insulin [12].

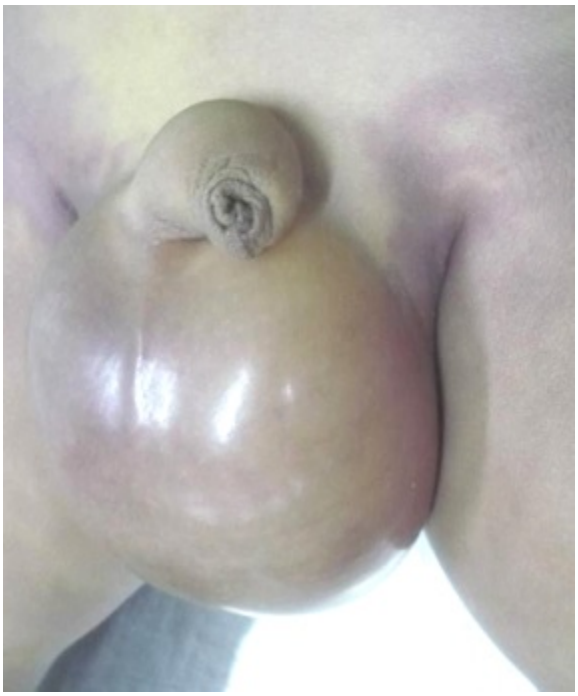

Fig. (11-1). Hyperhydration-related scrotal edema.

Functional Disorders and Hormone-Induced Lesions

Hypogonadism with Aspermia and Sterility can be produced by several drugs (Table **11-1**) and is difficult to differentiate from primary hypogonadism [13].

Sexual Dysfunctions can occur in patients taking antihypertensive drugs (*e.g.,* guanethidine) or psychotropics. These dysfunctions include diminished libido, delayed orgasm, ejaculatory disturbances (especially in the case of antipsychotics), gynecomastia, impotence (especially when taking antihypertensives) and priapism (Table **11-1**). Guanethidine inhibits prostate sperm production [14, 15]. Male infertility/germ cells apoptosis can also be caused, in a dose-dependent manner, by cytotoxic agents such as cyclophosphamide [16].

Estrogen-Induced Disorders relate to inhibition of gonadotropin release from the hypothalamus. This can lead to testicular atrophy, decreased libido and gynecomastia. Under the microscope, progressive disappearance of spermatogonia and Leydig cells is characteristic. This is a reversible lesion (following drug cessation) but fibrosis of the seminiferous tubules can emerge [13].

Antiandrogens-Induced Disorders also relate to impairment of the hypothalamic-pituitary-testicular axis. Transient sexual dysfunctions are common, but testicular atrophy, gynecomastia and cardiovascular lesions are more rare than following estrogen use [13, 17]. Details regarding these drugs are presented in Chapter 15.

Gynecomastia can be induced by more than 55 drugs/drug groups (Table **11-1**) and 10-20% of all cases are drug-induced [18 - 21].

Table 11-1. Drug-induced lesions of the male genitalia and breast. Data from references [1 - 25].

ADR type	Drugs
Genital fixed drug eruptions	Antifungals (ketoconazole), antiparasitic agents (metronidazole, miconazole) quinine, sulfonamides, NSAIDs (ibuprofen), antimalarials, antibiotics (amoxicillin), antihistamines, steroids
Genital ulcers/necroses	NSAIDs, antimalarials, ACE inhibitors, beta blockers, lithium, salicylates, steroids, trans-retinoic acid, vasoconstrictors (terlipressin), tyrosine kinase inhibitors (*e.g.,* sunitinib), mTOR inhibitors
Isolated genital edema	ACE inhibitors
Suppression of testicular function (aspermia, hypogonadism, ejaculatory dysfunctions)	Antiandrogens, estrogens, cimetidine, cytotoxic drugs (cyclophosphamide), beta blockers, antiarrhythmic drugs, digitalis, spironolactone (aldactone), phenothiazine, salazosulfapyridine, reserpine, guanethidine, psychotropics, steroids, isoniazid

CHAPTER 12

Iatrogenic Pathology of Bone Marrow and Lymphoid Tissue

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Abstract: Bone marrow and lymphoid tissue can be damaged by medications or radiation and are particularly susceptible to injury in bone marrow transplant recipients. Iatrogenic bone marrow suppression is a common in-hospital complication, the therapeutic management of which is difficult. In patients with cancer, aggressive treatment usually induces bone marrow damage, but this can be prevented using specific colony-stimulating factors. Heparin-induced thrombocytopenia is a distinct lesion with unusual clinical features. Its two types of manifestation are presented in this chapter, together with other lymphoid tissue-specific iatrogenic disorders.

Keywords: Adverse drug reaction, Bone marrow, Chemotherapeutics, Iatrogenic, Infection, Lymphoid tissue, Radiation, Sepsis, Thrombocytopenia, Thrombocytosis, Thromboembolism, Thrombosis, Transplant.

INTRODUCTION

Iatrogenic lesions of the bone marrow are primarily induced by medications, radiation and drugs that are administered before bone marrow transplantation. These can also be complications of diagnostic and therapeutic procedures (lymphography, silicone implant, *etc*.).

DRUG-INDUCED LESIONS

Similar to other organs and systems, drug-induced lesions of the bone marrow occur as a result of direct toxicity, immune mechanisms or idiosyncrasy. The most common ADR is bone marrow suppression and subsequent granulocytopenia, aplastic anemia, thrombocytopenia or pancytopenia. Thrombocytopenia and hemolytic anemia can emerge through immune-mediated formation of antiplatelets antibodies.

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Suppression of Hematopoiesis

Drug-induced bone marrow suppression is histologically characterized by hypoplasia, aplasia, panmyelophthisis or myelofibrosis (atrophy of bone marrow hematopoietic tissue and its replacement with connective tissue). The specific drug-related side effects are presented in Table **12-1**.

Chloramphenicol is the main drug known to induce myelotoxicity, which is more pronounced in the erythroid series. In most patients, this involves a dose-related anemia with reticulocytopenia, decreased erythrocytes and erythrocytes precursors production, infrequent leukopenia and thrombocytopenia. This effect is reversible and occurs during treatment. The erythroid cell precursors decrease until the first day of treatment and begin to regenerate from the seventh day of treatment. Dose-independent erythropoiesis inhibition leads to aplastic anemia. This reaction is reported in 1:24,000-1:40,000 of users, occurs within weeks or months of treatment and is often irreversible. Chloramphenicol also inhibits ribosomal protein synthesis [1, 2].

Phenylbutazone is the second drug known to demonstrate dose- and time-dependent myelotoxicity. This drug, which is primarily used to treat pain and fever in horses and was historically prescribed in sports medicine, is no longer available in the United States. Phenylbutazone-related myelotoxicity primarily refers to the inhibition of granulocytopoiesis, but myelophthisis and aplastic anemia can also be induced. Regarding its role in carcinogen-inducing blood dyscrasia, it has been proven that the cytogenetic effect is possible only in extremely high doses and phenylbutazone is thus not considered a carcinogenic substance in humans [3 - 5].

Chemotherapeutics induce dose-related leukopenia, emerging after the first or second cycle of administration. Thrombocytopenia and aplastic anemia can also be induced. The combination of chemotherapeutic drugs increases the risk of leukopenia and bone marrow aplasia with subsequent risk of infections, sepsis, hemorrhages, *etc*. (Fig. **12-1**). For example, the combination of paclitaxel and carboplatin induces anemia and neutropenia in about half of patients. Despite this, grade 3-4 toxicity occurs in fewer than 15% of such patients and can be prevented through administration of granulocyte colony-stimulating factor. Due to the fact that cisplatin is highly myelotoxic, there is a tendency to use carboplatin instead [1, 6].

Fig. (12-1). Spleen mycotic granulomas in an immunosuppressed patient.

Antithyroid (thyreostatic) Drugs can produce leukopenia and, more rarely, anemia, thrombocytopenia, agranulocytosis (0.25-1.75% of patients) and myelophthisis. The side effects can be dose-dependent or induced through idiosyncrasy [7, 8].

Anticonvulsant/antiepileptic Drugs can induce myelotoxicity, but this dose- and time-dependent side effect is rare. Neutropenia, agranulocytosis and panmyelopathy have also been reported. The most common consequences are opportunistic infections (*e.g.,* Clostridium difficile) and sepsis [1, 9 - 13].

Besides the above-mentioned drugs, myelotoxicity can also be induced by heparin, PPIs, antidepressant drugs, *etc*. Some vitamin K antagonists, such as ***fluindione***, can lead to agranulocytosis within one month of the initiation of treatment [14]. ***Azathioprine***, used for inflammatory bowel diseases, may induce fatal myelotoxicity, even after standard dosing [15]. ***PPIs*** can induce thrombocytopenia and anemia in a dose-dependent manner [16, 17]. ***Antidepressant selective serotonin reuptake inhibitors,*** such as sertraline, can cause coagulation abnormalities [18].

Drug-Induced Hemolytic Anemia is uncommon in daily practice, but its incidence has increased in recent years as a result of the widening therapeutic arsenal. It can be produced by several drugs (Table **12-1**), including NSAIDs (*e.g.,* nimesulide), antibiotics (meropenem, dapsone, *etc*.), long-term adalimumab treatment (in patients with psoriasis), chloramphenicol, nitrofurantoin, furazolidone, phenacetin, phenothiazine, salicylates, sulfonamides, *etc.* [1, 19 - 21]. Dose-dependent hemolytic anemia is induced by intravenous immunoglobulin in fewer than 0.5% of patients [22].

CHAPTER 13

Iatrogenic Pathology of the Skin and Subcutaneous Tissue

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Abstract: The skin and liver are the most common organs affected by the side effects of drugs. Drug-related damage to the skin and subcutaneous tissue is presented in detail in this chapter. Benign lesions include contact dermatitis and eczematous eruptions. Severe drug-induced injuries include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), acute generalized exanthematous pustulosis, bullous dermatoses and other hypersensitivity syndromes. The specific characteristics and responsible agents of these conditions are offered in tables in this chapter, and particular types of drug-induced lesions are also presented. A significant part of the chapter focuses on the effects of targeted cancer therapies on the skin and subcutaneous tissue. Granulomas and vaccine-induced lesions are also examined.

Keywords: Adverse drug reaction, Allergy, Antibody, Contact dermatitis, Dermatosis, DRESS syndrome, Eczema, eruption, Hyperpigmentation, Hypersensitivity, Iatrogenic, Pustulosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Vitiligo.

DRUG-INDUCED LESIONS

Of all the organs and tissue of the human body, the skin and cutaneous annexes are the systems most commonly affected by ADRs. The incidence of CU-ADRs is 2-3% of all hospitalized patients and even higher in females and elderly patients [1 - 3]. In pediatric emergency departments, the incidence is about 1% [4].

Most CU-ADRs are induced through hypersensitivity reactions, but direct toxicity, idiosyncrasy, metabolic enzymatic deficiencies and other mechanisms can also be involved.

About 98% of CU-ADRs are benign lesions (Tables **13-1** and **13-2**), with only 2% showing severe evolution (Tables **13-3** and **13-4**). In pediatric emergency

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departments, 53% of CU-ADRs are benign. These benign lesions occur primarily in children between two and 11 years of age, whereas severe CU-ADRs are more common in children between the ages of 12 and 15. The severe CU-ADRs of childhood are commonly induced by drug overdose [4].

Benign lesions include maculopapular and eczematous eruptions, exanthema, urticaria, erythema multiforme, erythroderma, lichenoid and lupus-like reactions, vesicular lesions, necroses, hemorrhages, hyperpigmentation, atrophy, alopecia, *etc.* [5].

Severe CU-ADRs are known to have potential lethality or to produce lifelong sequelae [5, 6]. They are immune-mediated by the drug-antigen/HLA-T-cell receptor complex and genetic susceptibility is a major component of their occurrence [6, 7]. Elderly patients and carriers of HLA-B*15:02, HLA-B*58:01, HLA-B*59:01 and HLA-B*13:01 present an increased expression of cytotoxic cytokines in serum and tissues, thereby being more predisposed to develop severe CU-ADRs [3, 8]. Severe CU-ADRs include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), linear immunoglobulin A (IgA) bullous dermatosis, acute generalized exanthematous pustulosis (AGEP), and the risk of pseudolymphoma, lymphoma and other tumors [7, 9 - 11].

Benign Lesions

Allergic Contact Dermatitis can be induced by cosmetics, drugs, laboratory chemicals, ultrasound gel, colophony, balsam of Peru, propolis, nickel sulfate, lanolin, pyocyanin, butylhydroquinone, surgical preparations of chlorhexidine and povidone-iodine, medical adhesives, topical neomycin/bacitracin, *etc.* [11 - 15].

Antiseptic bath emollients are frequently used in patients with eczema, which can induce local irritant reactions without significant clinical impact. In a few cases, large benzalkonium chloride-related ulcerations of the external genitalia were reported in young males, mimicking Fournier's gangrene [16].

In patients with carcinoma of the urinary bladder, granulomatous ulcerations at the base of the penis were reported one month following injection of intravesical BCG. In other patients, gangrene of the penis and perineum were seen within 24 hours of intravesical administration of mitomycin C, and penectomy was necessary three months after injection. The pathomechanism was the allergic contact reaction [17].

Eczematous Eruptions are primarily self-limited or present benign behavior. They can be induced by several drugs, including antimicrobial agents, NSAIDs, antihypertensives and anticonvulsants (Tables **13-1** and **13-2**). Exanthema (42%), erythema multiforme (10.5%) and vasculitis (9.5%) are the most common manifestations and are more severe in patients showing peripheral eosinophilia [18, 19].

Of all CU-ADRs produced by anti-infective drugs, radiographic contrast substances and NSAIDs, morbilliform exanthema (40%) and urticaria (23%) are predominant [2].

Eczematous dermatosis has been reported in patients with psoriasis treated with efalizumab [20], whereas acneiform eruptions can be induced by corticosteroids, iodides, bromides, anticonvulsants, isoniazid and immunosuppressants [21].

Table 13-1. Benign drug-related cutaneous lesions. Part I. Data from references [1-36].

Lesion	Drug class	Drug name
Eczematous eruptions	Antibiotics	Penicillins, Cephalosporins, Sulfonamides
	Diuretics	Thiazides
	Antihypertensives	Methyldopa, Beta blockers
	Anticonvulsants	Phenytoin, Phenobarbital, Carbamazepine
	Antidiabetics	Sulfonylurea
	Antipsychotics	Chlorpromazine Hydrochloride
	Other drugs	Quinidine, Bleomycin, Statins
Maculopapular eruptions	Antibacterial	Sulfonamides, Penicillins, Isoniazid
	Anticonvulsants	Phenytoin, Carbamazepine, Barbiturates
	Anti-inflammatory	NSAIDs, Sulfasalazine, Gold salts
	Antidiabetics	Sulfonylurea
	Antihypertensives	Captopril, Beta blockers
	Other drugs	Allopurinol, Bismuth, Carbimazole,
Urticaria	Anti-infective	Sulfonamides, Penicillins, Aminoglycosides, Cephalosporins, Vancomycin, Antifungals
	Anti-inflammatory	NSAIDs, Salicylates
	Antihypertensives	ACE inhibitors
	Contrast substances	Iodine-based radiographic contrast substances
	Vaccines	Animal serum, Desensitizing agents
	Other drugs	Anesthetic agents, Myorelaxants, Opiates, Dextrans

CHAPTER 14

Iatrogenic Lesions in Neurology

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Abstract: Iatrogenic neurological disorders can be induced by several factors, such as pharmacological agents prescribed for treatment or prevention (drug-induced neurological disorders [DIND]), complications of diagnostic and treatment procedures, like cerebral angiography or lumbar puncture, organ transplantation (related to the surgical procedure of transplantation, post-transplant immunosuppression, opportunistic infection or the inherent disorders that lead to transplantation), radiation therapy, *etc*. Iatrogenic neurological effects may be devastating due to the higher potential irreversibility of central nervous system, peripheral nervous system, neuromuscular junction (NMJ) and/or muscular system involvement. DIND represent the majority of iatrogenic neurological disorders. Drugs may directly induce neurological damage (through primary neurotoxicity, such as damage to the blood-brain barrier [BBB], disturbances of brain energy metabolism, ion channels/neurotransmitters disturbances, mitochondrial dysfunction, metabolite-mediated toxins, drug-induced selective cell death) or do so indirectly (cardiovascular, hematological or renal effects). Identification of DIND is important because early recognition and drug withdrawal can prevent irreversible damage. The numerous intrinsic risk factors for DIND should be well known by medical practitioners.

Keywords: Anticholinergic syndrome, Choreoathetosis, Dyskinesia, Dystonia, Encephalopathies, Intracranial hypertension, Meningitis, Myoclonus, Myopathies, Neuroleptic malignant syndrome, Neuromuscular junction, Neurotoxicity, Organ transplantation, Parkinsonism, Polyneuropathy, Radiation therapy, Serotonin syndrome, Sympathomimetic syndrome, Tremor.

INTRODUCTION

Iatrogenic neurological disorders (iatrogenic neurological adverse effects, iatrogenic neurology) are induced by: a) the administration of pharmacological agents prescribed for treatment or prevention (drug-induced neurological disorders); b) utilization of diagnostic and treatment procedures; c) organ transplantation. Iatrogenic neurological adverse effects may be devastating due to

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the higher potential irreversibility of central nervous system (CNS), peripheral nervous system (PNS), neuromuscular junction (NMJ) and/or muscular system (MS) involvements.

DRUG-INDUCED NEUROLOGICAL DISORDERS

The term "drug-induced neurological disorders" (DIND) refers to unintended/undesirable effects on the CNS, PNS, NMJ and/or MS caused by drugs or associated with drug use (inappropriate use, overdose of a drug or interaction with other drugs). DIND are important because early recognition and drug withdrawal can prevent irreversible damage. The drug may act directly (primary neurotoxicity) or indirectly *via* other systemic disturbances caused by the drug (secondary neurotoxicity).

The primary mechanisms of neurotoxicity are: a) damage to blood-brain barrier (BBB), facilitating the passage of drugs that normally do not cross the BBB; b) disturbances of brain energy metabolism (ATP synthetase inhibition, uncoupling/dissociation of oxidative phosphorylation, disturbances of oxygen consumption, enzymatic dysfunction, selective vulnerability of the nervous system); c) products of brain energy metabolism disturbances (calcium ions entry into the cells, oxygen free radical formation, excitatory amino acids); d) ion channels/neurotransmitters disturbances; e) mitochondrial dysfunction; f) metabolite-mediated toxins; g) drug-induced selective cell death.

Secondary neurotoxicity is the condition in which the CNS, PNS, NMJ and/or MS are affected by ADR-induced disorders in other organs/systems, such as the cardiovascular, respiratory, hepatic, renal, hematological and endocrine systems. Drug-related metabolic disorders and vitamin deficiencies are also common.

The main DIND-related mechanisms of neurotoxicity include oxidative stress, excitotoxicity, neuroinflammation, ubiquitin proteasome system, dysfunction of mitochondrial and/or neurotrophic factors.

The risk factors for DIND are patient-related (genetic predisposition, old age, history of neurological disorders, degenerative brain disease, intracranial space-occupying lesions, brain damage, systemic diseases, pregnancy) or drug-related (high doses, drug-drug interaction, drug-disease interaction, rate of drug delivery, route of drug administration, drug withdrawal).

The treatment of DIND involves the immediate discontinuation of the suspected drug [1 - 4].

Drug-Induced Disorders of Consciousness

Consciousness (CN) is a state of awareness, or of being aware of an external object or something within oneself. Its disturbance includes the following main clinical consequences [3]:

Syncope (SN) is a sudden transient loss of CN and postural tone, usually lasting no more than 15 seconds. Drug-induced SN represents 2-9% of all patients with SN. It is a common event, reported as an ADR, and its relation to the drug is difficult to determine in most cases. SN and falls are often two concomitant side effects of drugs reported in elderly patients. The most common drugs inducing SN include analgesics, antineoplastics, cytokines (interferon-alpha), digitalis, drugs that produce postural hypotension, vasodilators, drugs and combinations that prolong the QT interval, hypnotic sedatives (depressants of the CNS), antidepressants, antipsychotics, antiparkinsonian drugs, antidiabetics, selective serotonin reuptake inhibitors and vaccines.

Somnolence (SM) is a state of a strong desire for sleep, or sleeping for unusually long periods.

Lethargy (LG) is a state of sleepiness, deep unresponsiveness, listless, tiredness, lack of energy, apathy and inactivity.

Stupor (ST) is the lack of critical mental functions and a level of consciousness wherein a sufferer is almost entirely unresponsive, only responding to base stimuli such as pain.

SM, LG or ST may be due to overdose of a drug that does not produce any impairment of consciousness at therapeutic doses. The most common drugs that can induce SM, LG or ST include antidepressants, antiepileptics, antihistaminics, neuroleptics, analgesics and hypnotic sedatives.

Coma is a state of unconsciousness associated with neurological disorders in which the patient cannot be awakened, fails to respond normally to stimuli (pain, light, sound), lacks a normal sleep-wake cycle and does not initiate voluntary actions. Coma is a serious condition and a medical emergency. The most common drugs that can induce coma include hypnotic sedatives, anesthetics (propofol), antidiabetics (insulin, oral hypoglycemic agents) and drug-inducing encephalopathies (presented later in this chapter). Coma can also be a direct effect of prolonged use or overdose of barbiturates, benzodiazepines, opioids, tricyclic antidepressants, antiepileptics, *etc*.

CHAPTER 15

The Endocrinology and Iatrogenesis

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Abstract: Iatrogenicity is inherent to endocrinology, being a consequence of treatment (*e.g.,* use of thyroid hormones in large doses to suppress thyroid stimulating hormone [TSH] in thyroid cancer) or occurring due to a lack of patient compliance (*e.g.,* lack of adequate controls in chronic diseases, such as Hashimoto's chronic thyroiditis). Quite often, it is induced as a side effect of medicines (*e.g.,* long-lasting use of antithyroid agents or glucocorticoids). In this chapter, we review the most important iatrogenic effects, according to the main features of endocrinology. We present certain drugs that can trigger particular syndromes, such as the syndrome of inappropriate antidiuretic hormone secretion (SIAHS), along with preparations with pitressin and complications of treatment performed for pituitary adenomas, potential complications of drugs used to treat pituitary insufficiency in children and other specific features constituting required knowledge for medical practitioners. All therapeutic modalities of hyperthyroidism (medical, surgical, radioiodine) can cause iatrogenic pathology. For example, the euthyroid state is a sine qua non condition of thyroid surgery (except the thyrotoxic storm in advanced stages). Radioiodine treatment, in turn, has its own contraindications. Iodine-containing preparations can activate thyroid autonomies and aggravate autoimmune thyroiditis and overt hyperthyroidism. In hypothyroid elderly and cardiac patients, the thyroid hormone substitution must be applied only after initial cardiovascular treatment, in small, gradually increasing doses. In Addison's disease, indication of dietary salt reduction alongside glucocorticoid substitution, or the lack of increase in glucocorticoid dose in acute injuries, are serious iatrogenic complications.

Keywords: Acromegaly, Adrenal glands, Amiodarone, Antithyroid agents, Gonads, Hypercalcemia, Hyperthyroidism, Hypothyroidism, Octreotide, Thyroiditis.

INTRODUCTION

In endocrinology, iatrogenic lesions are inherent to the treatment of disease (*e.g.,* administration of large doses of thyroid hormones to substitute and suppress thyroid stimulating hormone [TSH] in the treatment of thyroid cancer), while in other circumstances, lesions appear due to lack of patient compliance (*e.g.,* lack of

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regular controls during treatment of diseases requiring long surveillance, as in the case of Hashimoto's chronic thyroiditis). Quite often, such lesions are induced as side effects of medicines (*e.g.,* long-lasting use of antithyroid agents or glucocorticoids), or by other therapeutic measures used in endocrinology or in associated diseases. In this chapter, the most important iatrogenic effects from the perspective of endocrinology will be reviewed.

IATROGENIC PATHOLOGY OF THE HYPOTHALAMIC-PITUITARY AXIS

Schwartz-Bartter Syndrome

Also known as inappropriate ADH secretion or as the syndrome of inappropriate antidiuretic hormone secretion (SIADH), this condition can be triggered by drugs such as vincristine, digitalis, some diuretics, morphine, carbamazepine, chlorpropamide, clofibrate, clozapine, cyclophosphamide, phenothiazines, tricyclic antidepressants, anesthetics, serotonin reuptake inhibitors, oxytocin, prostaglandin synthesis inhibitors, nicotine, omeprazole, ACE-inhibitors and 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy", a psychostimulant and hallucinogenic drug). An iatrogenic disorder can develop when during the treatment of this syndrome (in its acute or chronic form), hyponatremia is corrected too quickly, triggering osmotic demyelination syndrome (spastic tetraparesis due to pontine demyelination, pseudobulbar palsy, dyskinesia) and diffusing the brain injury [1].

ADRs in Patients with Diabetes Insipidus

In the treatment of diabetes insipidus, rarely used preparations including pitressin (Pitressin^{R}, Pitressin tannate^{R}) can trigger, *via* a direct vasoconstrictor effect, coronary artery spasm, hypertension or abdominal colics. The primarily preferred drug is desmopressin, a synthetic analog of vasopressin in the form of nasal drops (Adiuretin^{R}, Minirin^{R}), or sublingual tablets (Minirin Melt^{R}). Chlorpropamide, carbamazepine and clofibrate are active in partial forms of central diabetes insipidus, but they are today considered outdated for this purpose (weak action, danger of hypoglycemia after chlorpropamide).

Complications Occurring in Patients with Pituitary Adenomas

Therapy-Related Complications

The general management of pituitary adenomas raises therapeutic problems related to neurosurgical, radiological and conservative treatments. Each of these can be associated with specific complications.

Neurosurgical Treatment – in addition to more complete removal of adenomas, the main objective of this treatment is to minimize pituitary and brain injuries related to intervention, realizing selective removal of adenomas. Therefore, total nonselective hypophysectomy is currently only practiced exceptionally, even in advanced forms, in preference for subtotal hypophysectomy in nonselective or even selective forms. The ideal solution is a selective adenomectomy. Regarding the surgical approach, the transsphenoidal method and microsurgery are expected, and only in forms in which the upper (to the hypothalamus) or lateral extension transcranial (transfrontal) approach is the treatment of choice.

Radiation Therapy exerts its pituitary effects very slowly (for 0.5-10 years and over) and induces many adverse events, primarily pituitary insufficiency and secondary brain tumors (glioma, meningioma). More recently, an increased incidence of cerebrovascular disease has been reported after radiotherapy, increasing the mortality rate of irradiated patients (in cases of acromegaly). Therefore, irradiation is only practiced in selected cases, whether or not combined with other therapeutics, the treatment details of which are beyond the scope of this work.

Stereotactic Radiosurgery is used to avoid adjacent brain tissue injury *via* more precise targeting. The radiation source may be a linear accelerator (linac), or cobalt (gamma-knife). Irradiation with heavy particles (*e.g.,* proton radiosurgery) can be achieved only in a few specialized centers, requiring a cyclotron. Radiosurgery may be applied when the tumor is relatively small and radiosensitive structures (optical pathways, the brainstem) are not in the vicinity of the lesion. The ideal target of radiosurgery is a small residual tumor, located in the cavernous sinus. If the tumor cannot be precisely located, fractional radiotherapy must be applied to the entire likely tumoral area.

Conservative Treatment for any histological type of pituitary adenomas will be discussed below.

ADRs and Other Complications

Prolactinoma and Hyperprolactinemic States – the dopaminomimetic *bromocriptine* is the most commonly used drug for patients with prolactinoma. We must take care that its dose is increased gradually, starting with low doses – typically 1.25 mg/day (in oral administration, after going to bed in the evening) – which may be increased to 5-7.5 mg/day. If this requirement is not met, a number of side effects will occur (these will be discussed below, in the section regarding treatment of acromegaly, which involves use of this drug in much higher doses, reaching 10-30 mg/day). These doses are very difficult for patients to support, and are not even tolerated by many patients. *Cabergoline* (Dostinex^{R}) is another D_2-

CHAPTER 16

Iatrogenic Pathology in Anesthesiology and Intensive Care

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Abstract: The iatrogenic pathology occurring in anesthesiology and intensive care is a consequence of errors made due to ignorance (the incapacity to identify suddenly appearing pathological situations), negligence (deficiencies in applying correct medical conduct) or clinical misjudgment. In the field of anesthesiology, this type of pathology comprises complications in pre-anesthetic, anesthetic and post-anesthetic periods, the consequences of pharmacological effects of the administered anesthetic drugs, technical complications related to airway security, anesthetic machine functioning and monitoring equipment, the anesthetic technique utilized and the differing reactivity of patients to the chosen anesthetic procedure. In intensive care, regarding critical care patients with multiple organ dysfunctions, the main source of iatrogenesis is represented by invasive maneuvers (mechanical ventilation techniques, monitoring, vascular approaches). To all these are added complications related to administered drugs, artificial nutrition, volemic therapy and the high risk of infection.

Keywords: Anesthetic drugs, Artificial nutrition, Fluid therapy, General anesthesia, Infection, Intensive care, Loco-regional anesthesia, Maneuvers, Mechanical ventilation, Oxygen therapy.

INTRODUCTION

Iatrogenic complications appearing in the ICU are defined as adverse effects or pathological situations that occur independently of the underlying disease. In the USA, it is estimated that 4% of hospitalized patients in ICUs experience iatrogenic complications and 14% of such complications contribute to death [1].

These complications can be fatal (being primarily responsible for patient death), life-threatening (requiring intensive care measures such as mechanical ventilation, hemodialysis, vasopressors and thoracotomy) or moderate (requiring routine monitoring and management) [2].

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There are three main ***types of errors*** that can induce iatrogenic pathology in the ICU [3]:

- *Ignorance* – failure to recognize an unusual pathological situation, which can lead to a failure to provide the appropriate treatment.
- *Negligence* – failure to comply with universally accepted standards (*e.g.,* noncompliance with aseptic measures, failure to ask about allergies).
- *Erroneous judgment* – exaggerated optimism, unjustified designation of emergency status, "fashion" therapy, perfectionism, abstention, insufficient deliberation, *etc*.

The relationship between drugs (Table **16-1**) or medical procedures (Table **16-2**) and pathological situations can be definite (certain consequence of intervention), probable (likely consequence of intervention), possible (intervention-related), conditional (patient-related) or uncertain (not meeting any of these conditions) [4]:

Table 16-1. Drug-related iatrogenic lesions occurring in the ICU.

Type of drug	Disorders
Diuretics	Hypokalemia, hyperkalemia
NSAIDs	Gastrointestinal bleeding
Oral anticoagulants	Bleeding
Fluids	Fluid overload
Antibiotics	Hepatitis, allergies
Anesthetics	Respiratory failure, cardiac failure
ACEs	Acute renal failure, dehydration
Miscellaneous	Coma, metabolic disorders

Table 16-2. Medical procedure-related iatrogenic diseases occurring in the ICU.

Type of procedure	Type of disorder
Cardiac catheterization	Arrhythmia
Central venous catheterization	Bacteremia, pneumothorax
Peripheral venous catheterization	Bacteremia
Urinary tract catheterization	Infection
Radiocontrast infusion	Acute renal failure
Radiotherapy	Enteritis, leukemia

COMPLICATIONS OF GENERAL ANESTHESIA

During the patient's premedication and general anesthesia, various complications can be drug-induced or can be caused by technical malfunctions in equipment and unexpected reactions of the patient's body.

Side Effects of Drugs Used in General Anesthesia

Drugs Used in Premedication

Benzodiazepines (diazepam), barbiturates and opioids can produce respiratory depression, especially in elderly patients [5]. Minor neuroleptics (promethazine) can induce hypotension, xerostomia, skin reactions, esophageal sphincter hypotonia, *etc*. [6].

Intravenous Anesthetics

Thiopental can produce cough, hiccups, laryngospasm, bronchospasm, allergic reactions, respiratory depression, tachycardia and vasodilation. Perivascular extravasation can be followed by severe tissue injuries. Unintentional intraarterial injection leads to the formation of thiopental microcrystals in arterioles, followed by platelet aggregation and risk of thromboembolism.

Etomidate can induce cough, hiccups, laryngospasm, bronchospasm and adrenal suppression. Venous thrombosis is more common in this case than following use of other agents [7].

Propofol induces hypotension (20% of patients), transient apnea and allergic reactions. The rapid growth of microorganisms can also be a consequence [8].

Droperidol exerts cholinergic and sympatholytic effects and produces extrapyramidal motor symptoms, but does not induce respiratory depression. Dysphoria can also be noted.

Ketamine produces hypersalivation, hypotension, tachycardia, restlessness and transient apnea. It can also induce vivid dreams, increased intracranial pressure and allergic reactions.

Fentanyl causes respiratory depression and severe chest wall rigidity, and increases the tone of the sphincter of Oddi.

In patients treated with monoamine oxidase inhibitors, ***pethidine*** can cause serious complications, potentially fatal, ranging from hypotension and respiratory depression to hypertension and hyperpyrexia, seizures and coma.

CHAPTER 17

Iatrogenic Pathology in Surgery

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Abstract: Surgical intervention remains a trauma for patients even given modern techniques and the use of highly specialized instruments. Any surgical maneuver can cause injuries and complications. The severity of such injuries is determined by the disease itself, the patient's comorbidities and the surgeon's experience. In this chapter, we present the iatrogenic complications arising following major surgeries performed openly or laparoscopically. In the first section, general complications, such as hemorrhage, fever, ileus and abscesses, are presented. Next, organ-related complications occurring during laparotomy, drainage of the abdominal cavity or abdominal wall reconstruction are described in detail. We then turn to the specific intra- and postoperative complications of various organs' surgical treatment due to erroneous surgery indications, vascular lesions and lesions of the neighboring organs. We describe complications in the surgery of the mediastinum, thoracic and abdominal cavity and describe the particularities of thyroid, lung, esophagus, stomach, small intestine, appendix, colon, pancreas, hepatobiliary tract and hernia surgery and postoperative parietal defects. Complications occurring as a result of laparoscopic intervention, erroneous indications or complications in performing pneumoperitoneum during insertion of the trocars are also presented. Finally, we consider the specific iatrogenic complications arising during minimally invasive bile, hiatal hernia, cardiac achalasia, spleen and morbid obesity (gastric sleeve and gastroplication) surgery.

Keywords: Abscess, Chylothorax, Duodenal stump insufficiency, Fistula, Hematoma of the scrotum, Hemoperitoneum, Hemopneumothorax, Mediastinitis, Pancreas, Peritonitis, Suture dehiscence.

INTRODUCTION

The severity of surgery-related injuries is directly influenced by the type of disease, the patient's comorbidities and the surgeon's experience. Unexpected complications may manifest after surgery, which can spoil the patient's prognosis and endanger his life. The surgeon thus faces a new pathology, which is often difficult to diagnose or treat because it is caused by the original disease or the surgical procedure used during treatment.

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GENERAL COMPLICATIONS

The purpose of the atraumatic, tissue-friendly surgical technique is to minimize tissue damage, preserve vascular and nervous integrity, and prevent additional injury. Thus, we can ensure optimal tissue regeneration and reduce the rate of intra- or postoperative complications.

Fever of unknown origin, pain, infections, anastomotic insufficiency and wound dehiscence appearing after surgery is often caused by nonuse of *atraumatic techniques*. The requirements for the application of atraumatic surgical techniques are: expertise in the field of surgical anatomy, biomechanics and physiology of wound healing, and an excellent knowledge of the application of special surgical tools used during surgery. These techniques prevail, especially, during tissue dissection, when blood-free anatomic target areas are created by dividing the tissues. In order to prevent complications, correct hemostasis and knowledge of the advantages and disadvantages of the preparation techniques, as well as their proper application, are required (sharp, dull, electrical, ultrasonic, *etc*.).

To remove the blood, whey and tissue fragments created in the surgical area, it may be necessary to use *drainage*. This, however, is not a substitution for atraumatic technique. The rate of drainage-related complications depends on the quality, size, location and timing of surgical tube use.

The *quality of suture* is also an aspect of the atraumatic technique, most trauma being caused by the inadequate use of surgical needles. Nowadays, the use of atraumatic needles is more common, yet the diameter of the needle, its profile (round, triangular) and thickness, as well as the quality of the thread (monofilament, multifilament, absorbable, *etc*.) are all important considerations. The *suture method* also affects the quality of the atraumatic technique. Knots in suturing with dense stitches cause tissue ischemia and necrosis.

Aggressive surgical maneuvers induce tissue trauma with further functional or morphological damage [1].

SURGERY OF THE MEDIASTINAL CAVITY

In this section, we will present the lesions related to surgery of the esophagus and thyroid gland.

Iatrogenic Lesions in Surgery of the Esophagus

Surgery of the Esophageal Diverticula

Diverticulectomy is indicated in symptomatic cases (dysphagia, regurgitation) and

not for incidentally identified pulsating diverticula. Surgery is also indicated in associated inflammation, hemorrhages and chronically aspirated food remnants with aspirated pneumonia or lung fistulae. Reflux disease can be resolved with anti-reflux surgery.

Complications of such surgery can be related to the *surgical technique* and relate to recurrence as a result of clogging the diverticulum or incomplete myotomy. Sutures applied to close the diverticulum's aperture may cause stenosis, which can induce increased pressure and, in turn, lead to suture dehiscence.

Intraoperative Injuries include the following main lesions: hemorrhages (injuries of the common carotid artery, inferior thyroid artery or jugular vein), injuries of the recurrent laryngeal nerve (with postoperative hoarseness) and perforation of surrounding organs (esophagus, stomach, spleen, liver, pleura, lung).

Postoperative Injuries include fistulae (especially for Zenker's diverticulum), dehiscence of the epiphrenic diverticulum (with life-threatening mediastinitis displayed with dyspnea, fever, retrosternal pain, pleural and mediastinal fluid accumulation), stenosis (with dysphagia) and diverticulum recurrence (errors in surgical technique) [1 - 4].

Surgery of Malignant Tumors of the Esophagus

Incorrect Surgical Indication for esophagectomy can be the result of weak investigation of the patient. Improper preoperative assessment of metastatic status is a relatively common error, esophagectomy not being recommended in advanced stages, when the tumor infiltrates the respiratory tract, recurrent laryngeal nerve, lung or thyroid, even in the presence of liver or distant metastases. For example, in one of our cases, we intended to remove a diaphragmatic tumor reported preoperatively in a CT scan. Intraoperatively, a huge tumor of the middle third esophagus with infiltration of the trachea carina was identified, changing the operative protocol. The patient died 12 days after the surgery. This case attests to the necessity of attentive evaluation of the patient and choice of surgical procedure based on the tumor stage and localization, the patient's status and comorbidities, as well as the surgeon's experience and skill.

There is no consensus on the radical surgical treatment for malignant tumors of the esophagus. For subtotal esophagectomy, three principles should be respected: transhiatal method (Orringer), transthoracic block dissection (Skinner), and "two fielded" lymph node dissection (Akiyama) [1, 5].

Errors Regarding the Surgical Technique are mainly related to the surgeon's experience. For potentially curative tumors, oncologic radicalism and preserving

CHAPTER 18

Iatrogenic Lesions in Obstetrics and Gynecology

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Abstract: Gynecological surgery is associated with general risks that also occur in general surgery, but specific lesions are frequently encountered. For example, due to the fact that the genital organs are closely related to the organs of the urinary tract, they can easily be injured. These injuries primarily include lesions of the urinary bladder and ureters, but intestinal and nerve damage can also occur. Regarding drugs, dose- and time-dependent effects are controversial. These effects include thromboembolic complications, myocardial infarction, cerebrovascular accidents and even the carcinogenic risk of development of an endometrium or breast cancer.

Keywords: Cancer, Drugs, Gynecological surgery, Gynecology, Hormonal therapy, Intestinal lesions, Menopause, Nerve lesions, Side effects, Urinary tract lesions.

COMPLICATIONS OF SURGICAL INTERVENTIONS

In addition to the risks of general surgery, gynecological surgery has some specific characteristics and risks.

Lesions of the Urinary Tract

Due to the fact that the genital organs are closely related to the urinary tract, the urinary bladder is especially vulnerable to injury during gynecological surgery. It can be damaged in the process of opening the peritoneal cavity if the lower angle of the medial subumbilical incision is adherences between the bladder and the anterior abdominal wall can also cause its injury. The bladder can also be injured during total hysterectomy, as it is necessary to push the bladder down when performing this surgery. Another risk factor is preoperative radiotherapy for pelvic tumors. Although rare, surgical treatment of genital prolapse can also be associated with bladder injuries. These lesions should be sutured during surgical intervention, although minor lesions can heal spontaneously. Undetected lesions can cause uroperitoneum, peritonitis or vesico-vaginal fistulae. In some cases,

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nonabsorbable suture material can accidentally be passed through the bladder wall and the urothelium during hysterectomy. This can act as a nucleus for the formation of foreign body granulomas or urinary sectioned too close to the symphysis. In patients with previous surgical interventions (*e.g.,* cesarean section), calculi [1].

Lesions of the ureter are not so common but more serious complications. Based on a large body of data, it has been proven that at least one ureter is damaged in every 200 hysterectomies. Moreover, 50% of all iatrogenic ureter injuries occur during gynecological surgery, especially the surgery of cervical cancer (Wertheim's hysterectomy). Minor lesions can go unidentified during surgery and are associated with postoperative complications, such as macroscopic hematuria, ureterovaginal fistulae or urinary leak through the wound during micturition. Postoperative treatment of ureteric lesions is usually performed by urologists [2 - 4].

Intestinal Lesions

These lesions primarily occur during the opening of the peritoneal cavity, being caused by the presence of adhesions between the intestines and anterior abdominal wall in patients with previous laparotomies. They can also occur during laparoscopic interventions, especially during insertion of the trocars. Large bowel injuries are severe complications of laparoscopic surgery that are reported in 0.62-1.6/1000 laparoscopy cases. The treatment involves simple suture or segmental resection of the bowel in large lesions or perforations. Rectal lesions can occur during delivery (expulsion of the presenting part) or during the postpartum period (repair of perineal tears) [5, 6].

Nerve Injuries

These injuries occur in 1.1-1.9% of patients undergoing gynecological interventions. The main causes are malpositioning of the patient, incorrect placement of self-retaining retractors, hematoma formation, direct nerve entrapment and nerve transaction.

Although it is more aesthetic, the transverse Pfannenstiel laparotomy is associated with a greater risk of nerve lesions than median incision. The abdominal wall can potentially lose tone and become flaccid. Damage to the obturator nerve can occur during radical surgery, usually without significant consequences. Lesions of the genitofemoral nerve or ilioinguinal nerve can cause paresthesia of the vulva and inner thighs.

During vaginal surgery, the lower limbs of the patient are immobilized and the knee joints lean on metallic supports. In prolonged interventions or prolonged compression (*e.g.,* if the assistant leans on the knee of the patient), paralysis of the peroneus nerve can arise [7, 8].

ADVERSE DRUG REACTIONS IN OBSTETRICS AND GYNECOLOGY

In gynecological practice, hormonal treatment represents the most common prolonged treatment, with controversy regarding the risk-benefit ratio. Further details regarding these drugs are presented in Chapter 10.

Oral Contraceptives include estrogen and a progestin derivative. The estrogen component is ethynyl estradiol, but many progestin derivatives are available, involving several side effects, especially virilization. The side effects of contraceptive pills especially relate to their procoagulant properties. Thromboembolic complications are caused by the estrogenic component and emerge in 80/100,000 females taking a daily dose of ethynyl estradiol below five micrograms. At higher doses, this risk increases to about 112/100,000. The risk of myocardial or brain infarction is twice as high as that of nonusers, and even higher again in smokers. Considering these risks, there is a constant struggle to reduce the hormonal doses in contraceptive pills, the monthly dose being today lower than the daily dose used at the beginning of the 1960s [9, 10].

Hormone Replacement Therapy in Menopausal Females aims to abolish estrogen deficiency and prevent osteoporosis. However, this replacement is controversial. Monotherapy with estrogens proved to have a carcinogenic effect on the endometrium and breast. As a result, progestin components (with supposed protective effect on breast cancer) were added to these medications for some time. Nevertheless, some patients later developed breast cancer and the idea was abandoned. Moreover, synthetic progestins seem to stimulate secretions activity in rat endometrium and increase estrogens synthesis in the breast. In large multicentric trials, it has been shown that 41 of 10,000 women who used combined hormone replacement therapy in menopause presented noticeable time-dependent complications (eight with invasive breast cancer, seven with myocardial infarction, eight with pulmonary embolism, eight with brain infarction and 10 with peripheral vascular thrombosis). Considering the above-mentioned risks, initiation of hormone replacement therapy should be subject to a risk-benefit analys is [11, 12].

CONFLICT OF INTEREST

The authors confirm that this chapter content has no conflict of interest.

CHAPTER 19

Iatrogenic Lesions in Neurosurgery

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Abstract: Complications in neurosurgery can occur during diagnostic procedures, such as lumbar puncture, lumbar drainage, suboccipital cisternal tap or cerebral/spinal angiography, or during neurosurgical procedures. Severe complications during or subsequent to lumbar puncture are extremely rare and include brainstem herniation, infection, subdural hematoma and subarachnoid hemorrhage. Insertion of a catheter into the lumbar subarachnoid space to drain the cerebrospinal fluid (CSF) can also be followed by infection or overdrainage. The complications of cisternal tap include hemorrhage in the cisterna magna and piercing of the medulla oblongata that can cause cardiac or respiratory arrest. The iodine-based contrast agents used for cerebral angiography can cause allergic reactions and epileptic seizures. Iatrogenic complications during surgical procedures can occur at any stage pre-, intra- or immediately postoperative. Complications occur during patient positioning, rendering this step of paramount importance to the success of surgery. Infectious and cosmetic complications can occur during skin disinfection, incision of the skin of the scalp and surgical incision of the skull. Dural lesions can lead to cerebrospinal fluid leak or fistulae. Corticotomy or corticectomy should be realized cautiously and external to functional areas. Ligation or coagulation of brain vessels can lead to cerebral infarction (arterial or venous) with loss of cerebral function. Iatrogenic lesions in different regions of the brain lead to specific neurological manifestations. Lesions in the anterior fossa can lead to anosmia, abulia or behavioral alterations. Lesions in the middle fossa can lead to aphasia and motor deficits, while lesion in the posterior fossa can lead to cranial nerve deficits or coma.

Keywords: Anosmia, Aphasia, Brachial Paresis, Brain swelling, Brainstem herniation, Cerebrospinal fluid fistula, Chemical external otitis, Corticotomy, Duraplasty, Hearing loss, Ischemic stroke, Lumbar puncture, Meningitis, Osteonecrosis, Skull deformities, Thalamic infarction, Tonsillar herniation, Venous air embolism, Venous infarction, Ventriculitis.

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IATROGENIC LESIONS DURING DIAGNOSTIC PROCEDURES

Lumbar Puncture

In adults, the conus medullaris is located rostral to the termination of the thecal sac, being situated at the level of the L1-L2 vertebral bodies in the majority of cases. High (T12-L1) or low (L2-L3) variants of the conus medullaris are also encountered. A safe lumbar puncture should be realized at the level of the intercristal line (L4-L5). Following puncture, the overall risk of disabling or persistent symptoms is 0.1-0.5% only [1]. Severe complications are extremely rare and include brainstem herniation, infection, subdural hematoma and subarachnoid hemorrhage [2]. Tonsillar herniation can be acute, as in the case of an intracranial mass or a chronic lesion. Chronic herniation, also called acquired Chiari I malformation, is especially commonly reported following multiple traumatic lumbar punctures. Other possible complications are the following: infection (*e.g.,* spinal meningitis), spinal headache (usually positional), spinal epidural hematoma (usually associated with coagulopathy), spinal epidural collection of the cerebrospinal fluid (CSF), transplantation of the epidermal tissue *via* the needle with further development of a tumor, nerve root lesion by the needle (which can cause transient radicular pain), intracranial subdural hematoma or hygroma and sudden hearing loss. The latter may occur due to the drop in perilymph pressure through the cochlear aqueduct [1 - 3].

Lumbar Drainage

Insertion of a catheter into the lumbar subarachnoid space for the purpose of draining the CSF can be followed by: infection, overdrainage (if the drainage bag is situated too low), disconnection of the catheter and pneumocephalus. The latter can occur if the drainage occurs below the site of the CSF fistula and the air can be drawn through the fistula tract.

Cisternal Tap

This is an invasive procedure performed to achieve suboccipital access to the cisterna magna. It is usually realized with the patient in a sitting position with their neck flexed. The distance from the skin surface to the cisterna magna is about 4-6 cm, and from the dura to the medulla is 2.5 cm. Due to the tenting of the dura, the needle may infrequently touch the medulla. Peri-invasive complications include hemorrhage in the cisterna magna (due to perforation of a large vessel) and piercing of the medulla oblongata, which can cause cardiac or respiratory arrest [4].

Cerebral Angiography

This represents the gold standard in the diagnosis of cerebral vascular malformations (brain aneurysms, arteriovenous malformations, dural fistulae, *etc*.). Before Seldinger's technique was developed, cerebral angiography was realized through a direct carotid tap, meaning that bleeding to the puncture site could lead to a local compressive hematoma and respiratory distress. With Seldinger's technique, the usual puncture site is the femoral artery. Traumatic tap at this site can cause local hematoma that can extend into the retroperitoneal space. Transient femoral nerve injuries may also occur. The iodine-based contrast agents used for cerebral angiography can cause allergic reactions and epileptic seizures [5].

IATROGENIC COMPLICATIONS DURING SURGICAL PROCEDURES

Patient Position-Related Complications

Patient positioning is a key step during any surgical procedure and significant time must be spent to ensure that the position is as comfortable as possible for the patient, while offering, at the same time, the best approach for the surgeon. The sitting position for posterior fossa approaches can lead to venous air embolism, the mechanism of which involves perioperative negative pressure in the venous system of the head. Meticulous hemostasis, even for small bleedings, is mandatory [6]. The park bench position for cerebellopontine angle tumors can lead to brachial plexus elongation, while the lateral position can lead to contralateral axillary compression and brachial paresis. Head positioning is also of paramount importance. Forced rotation and flexion of the head can lead to impaired venous drainage, brain swelling and, in extreme situations, cervical luxation.

Lesions of the Skin and Scalp

During *skin disinfection*, surgical antiseptics can induce chemical conjunctivitis (if they reach the eye) or chemical external otitis (if they reach the ear). In cases of contact of the tympanum with iodine-based antiseptics, hearing impairment can arise.

Incision of the skin of the scalp should be performed behind the hairline in order to prevent unaesthetic scaring. Arcuate incisions of the scalp should have a fairly large pedicle in order to prevent scalp necrosis. In scalp lacerations, excision of the skin should be realized in a controlled manner in order to prevent skin defects. Tight suture of the skin can lead to scalp necrosis.

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