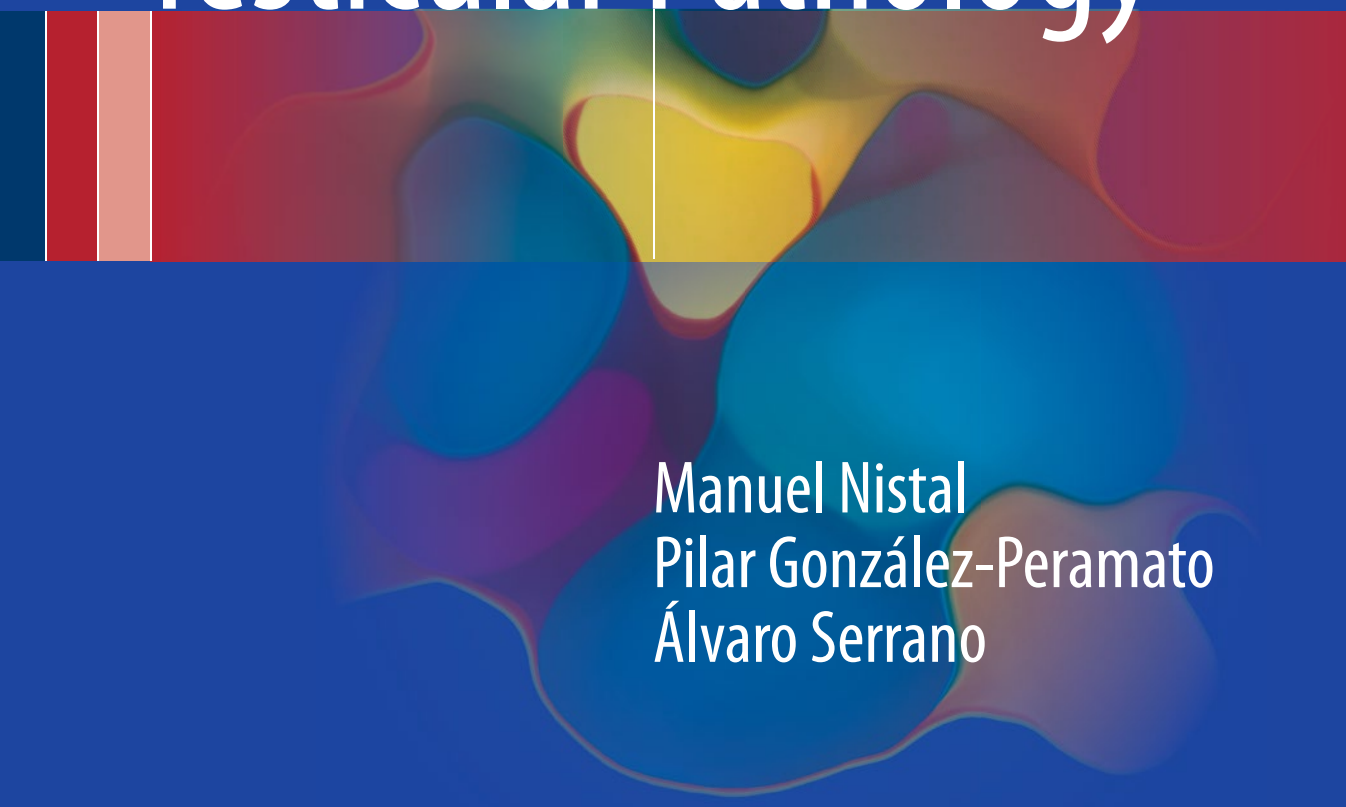
Clues in the Diagnosis of Non-tumoral Testicular Pathology



Manuel Nistal
Pilar González-Peramato
Álvaro Serrano

Springer

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Manuel Nistal
Universidad Autónoma de
Madrid (UAM)
School of Medicine
Madrid
Spain

Pilar González-Peramato
School of Medicine, Universidad
Autónoma de Madrid (UAM)
University Hospital La Paz
Department of Pathology
Madrid
Spain

Álvaro Serrano
University Hospital Clinico San Carlos
Department of Urology
Madrid
Spain

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To my wife, Piedad
To my children Rodrigo, Gonzalo, Beatriz, and Natalia
In memoriam, to my father Manuel

Manuel Nistal

To my husband, Alvaro
To my children Álvaro, Teresa, and Javier
In memoriam, to my parents Antonio and Pilar

Pilar González-Peramato

To my wife, Pilar
To my children Álvaro, Teresa, and Javier
In memoriam, to my father Lope

Álvaro Serrano

Preface

This book is a work based on the study and reflection of the authors about hundreds and hundreds of biopsies, surgical specimens, and autopsy material reported during more than 40 years in a university hospital, which treated testicular pathology – and precisely non-tumoral testicular and epididymal pathology – as a hobby. Therefore, this book does not pretend to be a compendium on this pathology, but a presentation of diagnostic problems that to be solved need knowledge on urology, andrology, pediatric gynecological endocrinology, and genetics apart from the usual pathological armamentarium. The success that the book *Testicular and Epididymal Pathology* by Nistal M and Paniagua R, editors, had in the 1980s has encouraged us to continue being specially interested in the non-tumoral testicular and epididymal pathology that has not raised a special interest in other pathology books.

What is the difference of this book from other books of pathology? In the majority of the treatises, the non-tumoral testicular pathology is reduced to a few items where the pathologist does not seem to play an important role. Our purpose is to present the diagnostic problems from the morphology of the lesions and build the diseases and their differential diagnosis under this perspective. Although the book is written in a schematic form, details necessary to get a deeper knowledge of this pathology and its differential diagnosis are included.

The chapters have been selected considering three reasons: first, that the different fields of non-tumoral testicular pathology – genetic, malformative, developmental, functional, vascular, or inflammatory – would be represented; second, that the topics should present problems on their differential diagnosis; and, third, that the pathologies included in this book should be uncommon enough to make this book a highly consultable text to solve certain problems in non-tumoral testicular pathology.

The chapters have been divided in eight parts: genetic and developmental pathology of the testes, infertility, vascular pathology of the testes, inflammatory pathology, pathology of the rete testis, pathology of the epididymis, pathology of the vaginal tunica and paratesticular structures, and miscellanea.

Bearing in mind that in pathology images are as important as – or even more important than – text, figures have been carefully selected in each chapter. Furthermore, in many chapters, to stand out the main characteristics of the lesions or to ease the diagnostic process, a variety of diagrams or algorithms have been included. In addition, legends are straightforward.

The authors have to thank the important contribution along many years of many pathologists in the study of the cases presented in this book, either as pathologist in training or sending cases in consultation that have been kindly and enthusiastically given up. We also have to emphasize the unconditional support of our clinicians and surgeons without whose collaboration this book of clues on non-testicular and epididymal pathology couldn't have been written.

Madrid, Spain — Manuel Nistal
Madrid, Spain — Pilar González-Peramato
Madrid, Spain — Álvaro Serrano

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The authors would like to heartily thank the University Hospital La Paz, one of the first big hospitals in Spain, in which two of the authors have developed their professional activity for many years. Special thanks go to all staff members and residents of the Department of Pathology at University Hospital La Paz for their support and for bringing to our attention items and cases of special diagnostic and descriptive interest. We also express our appreciation and gratitude to technical staff of the Department of Pathology at University Hospital La Paz for their careful preparation of the slides shown in this book. We would also like to recognize with thanks the Universidad Autonoma de Madrid where we have carried out our teaching and research activity.

We would also like to express our deepest thanks and appreciation to a large number of colleagues, co-workers, and friends who throughout the years have generously contributed cases in consultation, many of which are very rare and hence precious materials.

Finally, we wish to acknowledge Ana Weyland for her invaluable help to improve the English grammar and syntax of our manuscripts to transform them into readable documents.

Manuel Nistal
Pilar González-Peramato
Álvaro Serrano

Contents

1 What Does the Presence of Seminiferous Tubules Inside the Tunica Albuginea Mean? 1
1.1 Structure of the Normal Tunica Albuginea 1
1.2 Persistence of Testicular Blastema. 2
1.3 Persistence of Seminiferous Tubules in Normal Tunica Albuginea 4
1.4 Ectopia of Testicular Parenchyma in the Normal Tunica Albuginea. 6
1.5 Ectopia of Seminiferous Tubules in an Ovarian-Like Stroma 7
References. 8

2 Disorders of Sexual Development from the Pathologist's Perspective 9
2.1 Introduction 9
2.2 Histological Classification 10
2.3 Types of Gonads. 11
2.4 True Agonadism. 13
2.5 Gonadal Dysgenesis with Classical Streak Gonad 14
2.5.1 Turner's Syndrome. 14
2.5.2 46,XX Pure Gonadal Dysgenesis. 14
References. 15

3 Clinical Syndromes Associated with Streak Gonads with Epithelial Cords 17
3.1 46,XY Gonadal Dysgenesis. 17
3.2 Syndromes Associated with 46,XY Gonadal Dysgenesis 21
3.2.1 Denys-Drash Syndrome. 21
3.2.2 Frasier Syndrome. 21
3.2.3 WARG Syndrome 21
3.2.4 Campomelic Dysplasia 22
References. 22

4 Clinical Syndromes Associated with Dysgenetic Testis 25
4.1 Introduction 25
4.2 Mixed Gonadal Dysgenesis 25
4.3 Dysgenetic Male Pseudohermaphroditism 27
4.4 Persistent Müllerian Duct Syndrome (PMDS) 27
References. 30

5 True Hermaphroditism (Ovotesticular DSD) 33
5.1 Introduction 33
5.2 Karyotype 33
5.3 Pathogenetic Theories 33
5.4 Phenotype 34
5.5 Gonadal Types 34
5.6 Types of True Hermaphroditism 38
5.7 Biological Behaviour of the Gonads 38
5.8 Patient Management 38
References 38

6 Usefulness of Histological Studies in Patients with the Androgen Insensitivity Syndrome 41
6.1 Introduction 41
6.2 CAIS in Fetal Age 41
6.3 CAIS in Prepubertal Patients 42
6.3.1 Histological Findings 42
6.3.2 Differential Diagnosis 43
6.3.3 Associated Pathology 43
6.4 CAIS in Pubertal and Adult Patients 45
6.4.1 Histological Findings 45
6.4.2 Associated Pathology 45
6.5 PAIS 47
6.6 MAIS 47
6.7 Tumors in AIS 48
References 48

7 Differential Diagnosis of Tumors in the Adrenogenital Syndrome 51
7.1 Introduction 51
7.2 Development of Tumors of the Adrenogenital Syndrome 51
7.3 Clinical and Laboratory Diagnostic Clues 52
7.4 Diagnostic Imaging 53
7.5 Histological and Immunohistochemical Clues 53
References 56

8 Fetal Gonadoblastoid Testicular Dysplasia: An Early Defect in Testicular Tubulogenesis 59
8.1 Introduction 59
8.2 Histology 59
8.3 Differential Diagnosis 60
8.4 Etiopathogenesis 62
References 64

9 Differential Diagnosis of Sertoli Cell Nodules 67
9.1 Introduction 67
9.2 Histology 67
9.3 Variability of Sertoli Cell Nodules 67

9.4 Differential Diagnosis 69
9.4.1 Sertoli Cell Nodules Versus Intratubular Large Cell Hyalinizing Sertoli Cell Neoplasia 70
9.4.2 Sertoli Cell Nodules with GCNIS Versus Gonadoblastoma 70
9.4.3 Sertoli Cell Nodules Versus Sex Cord Tumor with Annular Tubules (SCTAT) 73
9.4.4 Macroscopic Sertoli Cell Nodules Versus Sertoli Cell Tumors "Not Otherwise Specified" 74
References 74

10 Meaning of the Finding of Testicular and Paratesticular Calcifications 75
10.1 Testicular Calcifications 75
10.1.1 Testicular Microlithiasis 75
10.1.2 Macrolithiasis Separated from Any Intratesticular Mass 78
10.1.3 Tumor-Associated Calcifications 79
10.2 Paratesticular Calcifications 80
10.2.1 Calcifications of the Epididymis 80
10.2.2 Epididymal Stones 81
References 81

11 Helpful Data for Evaluating an Undescended Testis in Childhood 83
11.1 Hypothalamic-Pituitary-Testicular Axis 83
11.2 Basic Data to Evaluate an Undescended Testis 84
11.2.1 Clinical Data 84
11.2.2 Histological Data 85
11.3 Classification of Undescended Testis 89
References 90

12 The Most Frequent Histological Findings in the Adult Testis When Testicular Descent Was Performed in Childhood 93
12.1 Most Frequent Testicular Lesions Observed in Adulthood . . 93
12.2 Correlation Between Pre- and Postpubertal Biopsies 97
12.3 Associated Secondary Testicular Lesions in Adult Testes . . . 98
12.3.1 Obstruction 98
12.3.2 Varicocele 99
12.4 Summary of the Nature of Testicular Lesions 99
References 100

13 Testicular Dysgenesis Syndrome (TDS) 101
13.1 Concept of Testicular Dysgenesis Syndrome 101
13.1.1 Testicular Germ Cell Tumors 101
13.1.2 Cryptorchidism 101
13.1.3 Hypospadias 102
13.1.4 Infertility 102

13.2 Etiology of TDS . . . 102
13.3 Histological Findings in TDS . . . 103
References . . . 108

14 Differential Diagnosis of Macroorchidism . . . 111
14.1 Asymmetric Testicular Size: Compensating Hypertrophy . . . 111
14.2 Non-tumoral Macroorchidism . . . 111
14.2.1 Early Harmonious Development of the Testis: Gonadotropin-Dependent Precocious Puberty – Central Precocious Puberty (CPP) . . . 111
14.2.2 Dissociation of Tubular and Interstitial Development . . . 112
References . . . 119

15 Macroorchidisms Secondary to Functioning Tumors during Childhood . . . 123
15.1 Introduction . . . 123
15.2 Leydig Cell Tumors . . . 123
15.3 Sex Cord Tumors . . . 126
15.4 Adrenocortical Tumors . . . 127
15.5 Extratesticular HCG-Secreting Tumors . . . 128
15.6 Other Tumors . . . 128
References . . . 129

16 Value of Testicular Biopsy in Nonobstructive Azoospermia . . . 131
16.1 Tubular Hyalinization . . . 131
16.2 Sertoli Cell-Only Syndrome (SCOS) . . . 132
16.3 Mixed Atrophy . . . 134
16.4 Lesions of Basal and Adluminal Compartment . . . 135
16.4.1 Hypospermatogenesis . . . 135
16.4.2 Maturation Arrest . . . 136
16.5 Potentially Predictive Factors . . . 139
References . . . 139

17 Obstructive Mechanism Lesions Simulating Primary Testicular Lesions . . . 143
17.1 Histological Characteristics of the Obstructive Mechanism Lesions . . . 143
17.1.1 Qualitative Data . . . 143
17.1.2 Quantitative Data . . . 143
17.2 Mechanism of the Testicular Lesions . . . 147
17.3 Factors Affecting the Development of Testicular Lesions . . . 147
17.4 Differential Diagnosis Between Obstructive Mechanism Lesions and Primary Testicular Lesions . . . 149
References . . . 149

18 Fertility in Patients with Chromosome Abnormalities . . . 151
18.1 Numerical Chromosome Aberrations . . . 151
18.1.1 Klinefelter's Syndrome . . . 151
18.1.2 The XX Male Syndrome . . . 153

18.1.3 The XYY Syndrome 154
18.2 Structural Chromosome Aberrations 155
18.2.1 Structural Aberrations of the Autosomes 155
18.2.2 Structural Aberrations of the Sex Chromosomes . . 155
18.3 Y-Chromosome Microdeletions 156
References 159

19 Fertility Potential of Patients with Hypogonadotropic Hypogonadism 163
19.1 The Male Reproductive Axis 163
19.2 Classification of Hypogonadotropic Hypogonadism 163
19.2.1 Congenital Hypogonadotropic Hypogonadism (CHH) 164
19.2.2 Acquired Hypogonadotropic Hypogonadism (AHH) 166
19.3 Fertility Predictor Data 167
19.4 Treatment Methods 169
References 169

20 Ultrastructural Pathology of the Spermatozoa with Genetic Basis 171
20.1 Introduction 171
20.2 Microcephalic Spermatozoa 171
20.2.1 Globozoospermia: Round-Headed Spermatozoa Syndrome 171
20.2.2 Microcephalic Spermatozoa with Acrosome Hypoplasia 173
20.3 Macrocephalic Head Spermatozoa Syndrome: Large-Headed Spermatozoa 173
20.3.1 Spermatozoa with Multiple Flagella 173
20.3.2 Macrocephalic Spermatozoa Without Flagella . . . 174
20.4 Abnormal Head-Tail Attachment 174
20.4.1 Decapitated Spermatozoa/Acephalic Spermatozoa 175
20.4.2 Defects of the Connecting Piece 176
20.4.3 Separated Head and Flagellum: Decapitated and Decaudated Spermatozoa 176
20.5 Fibrous Sheath Dysplasia 176
20.6 Primary Ciliary Dyskinesia (PCD): Immotile Cilia Syndrome 177
References 179

21 Spermatic Cord Torsion and Infertility 183
21.1 Introduction 183
21.2 Physiopathology 184
21.3 Indicators of Testicular Salvage Ability 184
21.4 Causes of Infertility 187
21.5 Potential Protective Agents 187
References 189

22 Clues to the Analysis of Testicular Lesions in Infertile Patients with Varicocele 191
22.1 Varicocele and Infertility 191
22.2 Pathogenetic Mechanism 191
22.3 Clues to Interpret Testicular Lesions 194
References 198

23 Surgical Treatment of Varicocele 201
23.1 Indications for Varicocele Surgical Repair 201
23.2 Treatment Options 201
23.2.1 Open Surgery 202
23.2.2 Laparoscopic Surgery 204
23.2.3 Retrograde and Antegrade Embolization or Sclerotherapy of the Spermatic Veins 205
23.3 Results of Surgical Techniques 206
References 207

24 Testicular Involvement in Noninfectious Vasculitis 209
24.1 Polyarteritis Nodosa (PAN) 209
24.2 Henoch-Schönlein Purpura 210
24.3 Wegener's Granulomatosis 211
24.4 Giant Cell Arteritis 213
24.5 Thromboangiitis Obliterans (TAO) 213
24.6 Kogan's Disease 215
24.7 Behçet's Disease 215
24.8 Vasculitis Associated with Other Processes 215
References 215

25 Vascular Pathology Related to Extracellular Material Accumulation 219
25.1 Arteriolar Hyalinosis 219
25.2 Disseminated Intravascular Coagulation (DIC) 221
25.3 Amyloidosis 222
References 227

26 Interpretation of Testicular Non-granulomatous Lymphoid Infiltrates 229
26.1 Infiltrates Rich in Polymorphonuclear Leukocytes 229
26.1.1 Acute Orchiepididymitis 229
26.2 Infiltrates Rich in Lymphocytes 230
26.2.1 Primary Autoimmune Orchitis (Focal Orchitis) . . 230
26.2.2 Chronic Nonspecific Orchitis 231
26.2.3 Testicular Pseudolymphoma 231
26.3 Infiltrates Rich in Macrophages 232
26.3.1 Macrophages with Granular and Eosinophilic Cytoplasm 232
26.3.2 Macrophages with Clear Cytoplasm 234
26.4 Infiltrates Rich in Plasma Cells 236
26.5 Mast Cells and Infertility 237
References 237

27 Histological Basis for the Interpretation of Granulomatous Orchitis 241
27.1 Granulomatous Orchitis Destroying Testicular Architecture 241
27.1.1 Granulomatous Orchitis with Necrotizing Granulomas 241
27.1.2 Granulomatous Orchitis with Non-necrotizing Granulomas 244
27.1.3 Granulomatous Orchitis by Foreign Bodies 245
27.2 Granulomatous Orchitis Preserving Testicular Architecture 247
27.2.1 Idiopathic Granulomatous Orchitis (IGO) 247
27.2.2 Peritumoral Granulomatous Orchitis. Granulomatous Tubulitis 248
References 250

28 Rete Testis Dysgenesis as a Marker of Undescended Testis . . . 253
28.1 Normal Rete Testis 253
28.2 Rete Testis Dysgenesis 254
28.2.1 Definition 254
28.2.2 Histological Patterns of Dysgenesis of the Rete Testis 254
28.2.3 Relationship Between Dysgenesis of the Rete Testis and Other Primary Anomalies of the Undescended Testis 257
28.2.4 Differential Diagnosis 258
28.2.5 Situations in Which Dysgenesis of the Rete Testis Can Be Observed 259
References 259

29 Congenital Cystic Pathology of the Rete Testis 261
29.1 Cysts of the Rete Testis 261
29.2 Cystic Dysplasia of the Rete Testis 261
29.2.1 Definition 261
29.2.2 Histological Features 263
29.2.3 Differential Diagnosis 265
29.2.4 Associated Pathology 266
29.2.5 Treatment 267
References 267

30 Acquired Cystic Transformation of the Rete Testis (Cystic Ectasia of the Rete Testis) 269
30.1 Defense Mechanisms of the Testis Against Testicular Fluid Obstruction 269
30.2 Concept of Acquired Cystic Transformation of the Rete Testis (ACTRT) 270
30.2.1 Definition 270
30.2.2 Diagnosis 270
30.2.3 Differential Diagnosis of the Cystic Transformation of the Rete Testis 271

30.3 Histological Types of Cystic Transformation of the Rete Testis 271
30.3.1 Simple Cystic Transformation of the Rete Testis 271
30.3.2 Cystic Transformation of the Rete Testis with Epithelial Changes 273
30.3.3 Cystic Transformation of the Rete Testis with Crystalline Deposits 275
References 276

31 Acquired Pathology of the Rete Testis 279
31.1 Reactive Hyperplasia 279
31.2 Hyperplasia with Hyaline Globules 279
31.3 Adenomatous Hyperplasia of the Rete Testis 281
31.4 Lithiasis of the Rete Testis 283
31.5 Intracavitary Nodular Polypoid Calcifying Proliferations 284
31.6 Atrophy of the Rete Testis 284
References 285

32 Congenital Cystic Pathology of the Epididymis 287
32.1 Cysts 287
32.1.1 Histological Types 287
32.1.2 Peculiar Findings in Epididymal Cysts 292
32.2 Cystic Dysplasia of the Epididymis 293
References 295

33 Reactive Pathology of the Epididymis 297
33.1 Epididymal Ectasia 297
33.2 Paneth-Like Metaplasia 298
33.3 Ischemic Granulomatous Epididymitis 299
33.4 Epididymal Metaplasia 301
33.4.1 Prostatic Metaplasia 301
33.4.2 Squamous Metaplasia 302
References 303

34 Metaplasias of the Testicular Tunica Vaginalis 305
34.1 Histological Types of Metaplasia 305
34.1.1 Urothelial Metaplasia 305
34.1.2 Müllerian Metaplasia 305
34.1.3 Mucinous Metaplasia 307
34.1.4 Squamous Metaplasia 308
34.1.5 Gastric Metaplasia 309
References 309

35 Reactive Mesothelial Hyperplasia Versus Mesothelioma 311
35.1 Histopathology: Types of Reactive Mesothelial Hyperplasia 311
35.1.1 Solid and Papillary 311
35.1.2 Pseudoinfiltrative: Florid Mesothelial Hyperplasia 311

35.2 Clinical Features . . . 312
35.3 Differential Diagnosis . . . 312
35.3.1 Mesotheliomas . . . 313
35.3.2 Metastasis of Adenocarcinoma . . . 316
References . . . 316

36 Paratesticular Tumor-Like Congenital Lesions . . . 319
36.1 Adrenal Cortex Ectopia . . . 319
36.2 Splenic Ectopia (Splenogonadal Fusion) . . . 320
36.3 Hepatic Ectopia (Hepato-gonadal Fusion) . . . 323
36.4 Orchidogastric Fusion . . . 324
36.5 Renal Parenchyma Ectopia . . . 324
References . . . 325

37 Paratesticular Tumor-Like Acquired Lesions . . . 327
37.1 Meconium Periorchitis . . . 327
37.2 Foreign Body Vaginalitis . . . 328
37.3 Scrotal Lithiasis . . . 328
37.4 Cholesterol Granuloma . . . 329
37.5 Vasitis Nodosa . . . 330
37.6 Sperm Granulomas . . . 331
37.7 Endometriosis . . . 332
37.8 Lipomembranous Fat Necrosis (LFN) of the Spermatic Cord . . . 332
37.9 Pseudosarcomatous Periorchitis . . . 333
37.10 Paratesticular Cyst . . . 334
37.11 Fibrous Pseudotumor (Nodular and Diffuse Proliferation) . . . 334
37.12 Sclerosing Lipogranuloma . . . 335
37.13 Smooth Muscle Hamartomas (Smooth Muscle Hyperplasia) . . . 336
References . . . 337

38 Intratesticular and Paratesticular Patterns of Mesonephric Remnants . . . 341
38.1 Structures Derived from Embryonic Remnants . . . 341
38.2 Histological Characteristics of the Mesonephric Remnants . . . 341
38.3 Testicular and Paratesticular Mesonephric Remnants . . . 342
38.3.1 Mesonephric Remnants in the Spermatic Cord . . . 342
38.3.2 Mesonephric Remnants in Hernial Sacs . . . 342
38.3.3 Mesonephric Remnants in the Testicular Hydatid . . . 342
38.3.4 Mesonephric Remains in the Tunica Vaginalis . . . 344
38.3.5 Intratesticular Mesonephric Remnants . . . 344
References . . . 347

39 Testicular Changes in Elderly Men 349
39.1 Introduction 349
39.2 Hormonal Changes with Age 349
39.3 Morphological Alterations of the Testes 350
39.3.1 Seminiferous Tubules 350
39.3.2 Interstitium 354
39.4 Mechanisms of Testicular Lesions 356
References 358

40 Treatment-Related Testicular Changes 363
40.1 Introduction 363
40.2 Testicular Function and Cancer Treatments 363
40.2.1 Surgery 365
40.2.2 Radiation Therapy 365
40.2.3 Chemotherapy 367
40.2.4 Potential for Fertility Following Cancer Treatment in Childhood 370
40.3 Estrogen and Antiandrogen Therapy 370
References 373

1 What Does the Presence of Seminiferous Tubules Inside the Tunica Albuginea Mean?

Manuel Nistal, Pilar González-Peramato, and Álvaro Serrano

1.1 Structure of the Normal Tunica Albuginea

Together with the interlobular septa, the albuginea forms the structures of the testicular parenchyma support. They divide the testis in 250 lobules with a pyramidal shape. The base, peripheral, is formed by tunica albuginea and the sidewalls by interlobular septa. The lobules, the seminiferous tubules, and the interstitium are located inside with Leydig cells outstanding in the latter. Through the apex the seminiferous tubules are the continuation of the tubuli recti, i.e., the initial part of the rete testis.

The tunica albuginea is formed early, immediately after the appearance of the primitive testis cords [1]. One fibrous basement membrane immediately under the coelomic epithelium as a result of cell differentiation of coelomic epithelium and testicular interstitium and possible migration of extragonadal cells is formed [2, 3]. In the newborn the structure closely resembles that of an adult. The early formation of the tunica albuginea seems to be under the control of the anti-Müllerian hormone produced by Sertoli cells [4].

Histology

In the adult, the tunica albuginea has three layers: the outer layer (tunica vaginalis) is thin and consists of a mesothelial lining resting on a basement membrane. The middle or thicker layer is dense connective tissue, and the inner layer (tunica vasculosa) is loose connective tissue. In the middle layer, the cells, fibroblasts, myofibroblasts, and smooth muscle cells and the fibers, mostly collagenous fibers, are arranged in planes parallel to the surface [5] (Fig. 1.1). From the outer to the inner layers, the amount of collagen fibers decreases, whereas the number of cells increases. This phenomenon is parallel to changes in the phenotype of contractile cells. A secretory phenotype predominates in the most superficial zone and a contractile phenotype in the deepest one [6]. The density of the smooth muscle cells varies in different parts of the tunica albuginea, being higher in the lower pole and the posterior edge of the testicle. Among muscle cells and in their immediate apposition, axon varicosities containing vesicles are distributed suggesting functional innervations of the smooth muscle. The tunica at the lower pole of the testis is crossed by arteries, and nerves that pierce the tunica vasculosa and advance along it reach the parenchyma through the interlobular septa, and in the opposite direction is crossed by veins and lymphatics.

The tunica albuginea, like all testicular structures, is subject to changes throughout life. These changes affect the thickness as well as cell differentiation and the degree of collagenization. During the first 6 years, the thickness hardly changes although a progressive collagenization of the outer part of the middle layer occurs. From

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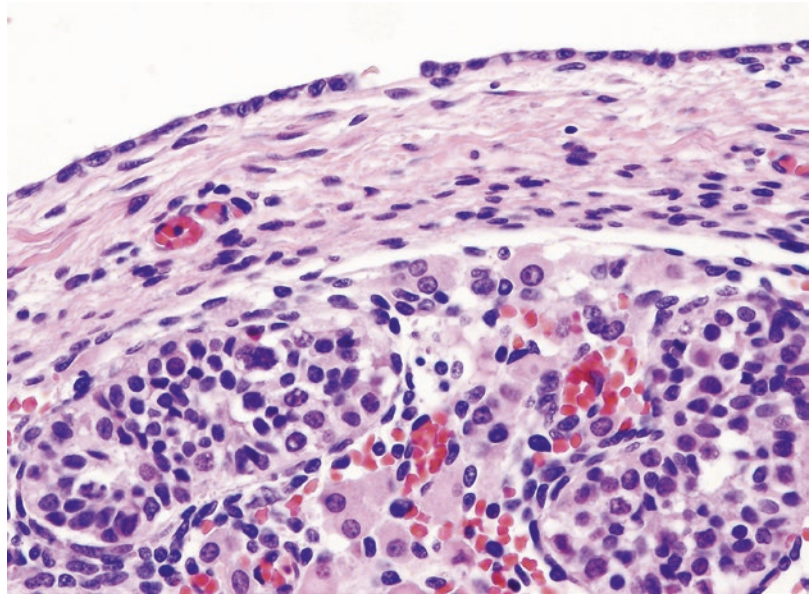

Fig. 1.1 Testis of a newborn baby. The tunica albuginea shows mesothelial lining. Beneath there are two layers, the external one is poorly cellular with abundant collagenous fibers while the internal layer is more cellular. Two sections of seminiferous tubules and abundant Leydig cells are recognized in a deeper location

these 6 years onward, the thickening process continues and accelerates in puberty and goes from 400 microns in young men to over 900 microns in some older men.

Physiology
The functions of the tunica albuginea are multiple. To classic functions such as protection of testis against traumas or acting as a semipermeable membrane that produces the fluid of the vaginalis cavity, a contractile function is added. It is spontaneously able to contract and relax due to the presence of abundant contractile cells showing high concentrations of guanosine monophosphate (GMP), and thus the testicular size and the propelling of sperm from the seminiferous tubules into the head of the epididymis are regulated [7]. This process is dominated by the adrenergic system in association with a smaller purinergic component [8].

1.2 Persistence of Testicular Blastema

Testicular blastema represents the next step in male differentiation of gonadal blastema. It is identified by the presence of poorly defined immature sexual cords with germ cells and little mesenchyma without differentiated Leydig cells [9, 10]. It is the result of the expression of *SRY* gene by Sertoli cells that trigger the expression of other Sertoli cell-specific genes that cause Sertoli-primordial germ cell aggregation and proliferation of Sertoli cells in the underlying mesenchyme [11].

The presence of testicular blastema has been observed in both testes of three newborn babies from a total of 3228 consecutive autopsies at the La Paz University Hospital [12]. These patients had the following conditions: one was the result of a spontaneous abortion due to chorioamnionitis; one was an elective abortion due to a neural tube defect, omphalocele, and asymmetrical arthrogryposis; and the third case had trisomy 18 and the classic features of the Edwards' syndrome.

Histology The persistence of testicular blastema (PBT) takes the form of a crescent, is located in the upper pole of the testis in the vicinity of the epididymis, and occupies an area of several millimeters. There is no tunica albuginea at this level, although the rest of the tunica and the testicular parenchyma and epididymis are normal for the age.

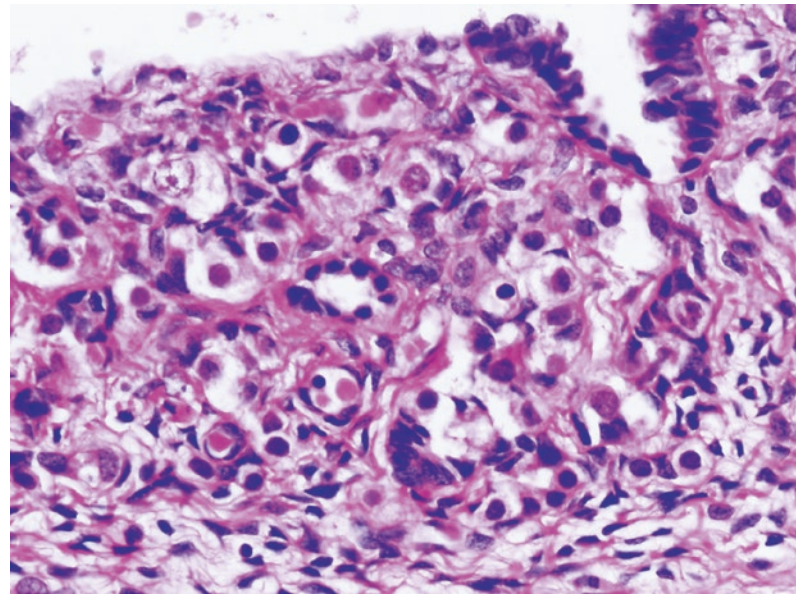

Fig. 1.2 Testicular blastema. Under the coelomic lining formed by cylindrical cells, there is a cellular proliferation in which two cell types are identified; one, the less abundant, has a large and clear cytoplasm; the other is smaller and tends to be arranged around the former cells

The appearance of PBT in low power field is a densely cellular tissue without internal architecture in which at least two cell types are distinguished; one, the most abundant, in continuity with the lining epithelium is polygonal to oval-shaped cells with scant cytoplasm and prominent nucleoli; the other is larger with clear cytoplasm, vesicular nucleus, and central nucleolus in small numbers randomly distributed among the above (Fig. 1.2).

Immunohistochemistry Immunohistochemistry techniques show that the first cell type is derived from the lining epithelial and is being incorporated into the lesion. These cells are strongly positive for cytokeratin AE1/AE3 and calretinin as the epithelial lining. This positivity decreases as the cells take deeper positions until eventually disappearing. The second cell type is represented by primordial germ cells or gonocytes for their positive expression of PLAP and OCT3/4. When the lesion is studied with immunostaining for laminin and collagen IV, a startup organization is revealed inside, unsuspected with H&E, of short, rough, and thick cords surrounded by laminin and collagen IV that are in continuity with the coelomic epithelium. Peritubular myoid cells stained for smooth muscle actin or Leydig cells expressing calretinin are not observed.

The immunohistochemical study supports an early testicular differentiation. Cellular cords probably correspond to pre-Sertoli cells that begin to synthesize components of the basal lamina as laminin and collagen IV, but these cells are still unable to differentiate into myoid cells to form tunica propria, and neither are they able to induce Leydig cell differentiation, both functions related to early differentiation of Sertoli cells [13, 14].

Differential Diagnosis The most important differential diagnosis of this lesion arises with the persistence of "undifferentiated gonadal tissue" (UGT) and secondly with ovotestes. The UGT is a characteristic lesion of patients with disorders of sexual differentiation (DSD) with streak gonads with epithelial cords, dysgenetic testis, streak testis, and ovotestis. UGT represents a gonad in which the arrest of further differentiation is even earlier as ovarian or testicular differentiation is not recognized and does not take a surface distribution like a band in the gonad. These testes, in opposition to those who are UGT carriers, do not have a higher incidence of transformation into gonadoblastoma.

PBT shares with ovotestes the peripheral arrangement on a crescent in a testis but the difference is the following: in the ovarian component of ovotestes there is no tubular organization; the size of germ cells, oocytes, is much higher than that of gonocytes; among female germ cells, there is an abundant stroma similar to that in the ovarian cortex, which is absent in PBT; PBT is not clinically associated with DSD.

Biological Behavior It is very likely that the evolution of PBT, although very delayed in time, would be toward testicular parenchyma both with seminiferous tubules and Leydig cells. The last lesion commented has been observed in infants, children, and adults in this same area of the testis as ectopia of the seminiferous tubules with normal tunica albuginea.

1.3 Persistence of Seminiferous Tubules in Normal Tunica Albuginea

These are seminiferous tubules in formation, directly in connection with the mesothelium externally lining the albuginea. There are short and twisty epithelial cords with scarce interstitium. The extent of the surface of the tunica affected is very variable, and it is not exceptional that almost all of it is involved. It is noteworthy that in all cases under this lesion, the normal structure of the deepest part of the tunica and the delimitation with testicular parenchyma remain clear (Figs. 1.3, 1.4, and 1.5).

Histology Forming seminiferous tubules are constituted by both Sertoli cells, the most numerous, and by gonocytes, numbering two or three per tube. They are surrounded by a thin basement membrane with linear positivity for collagen IV and laminin and externally by a layer of myoid cells. Some Leydig cells develop between the tubular formations.

Immunohistochemistry Immunohistochemistry allows following all the steps of this newly formed tubules. The onset of formation of the seminiferous tubules begins at the surface with changes in morphology and immunophenotype of the mesothelium. The usually cuboidal or squamous epithelium becomes cylindrical and loses the expression of characteristic mesothelial cytokeratins except for cytokeratin 18. Seminiferous tubules, in the form of epithelial

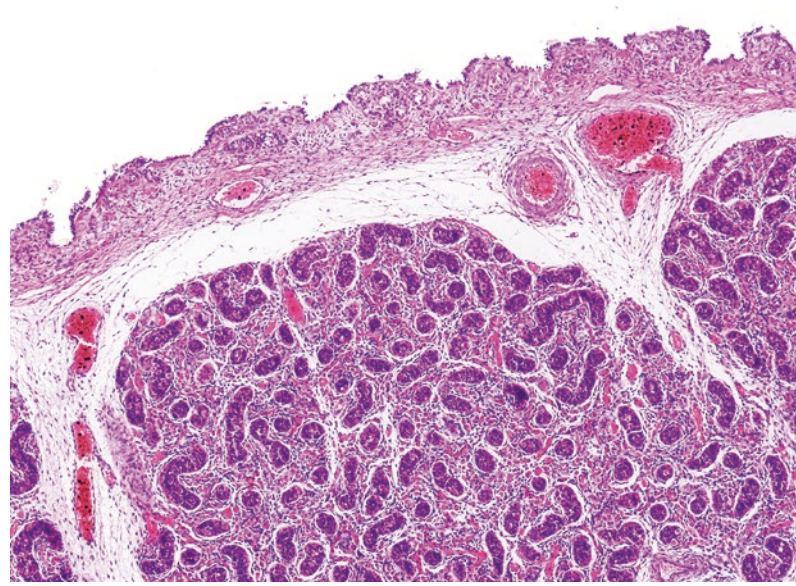

Fig. 1.3 Persistence of seminiferous tubules in formation in the surface of tunica albuginea. The outer contour of the testis has a wavy surface caused by protrusions of different groups of seminiferous tubules in development

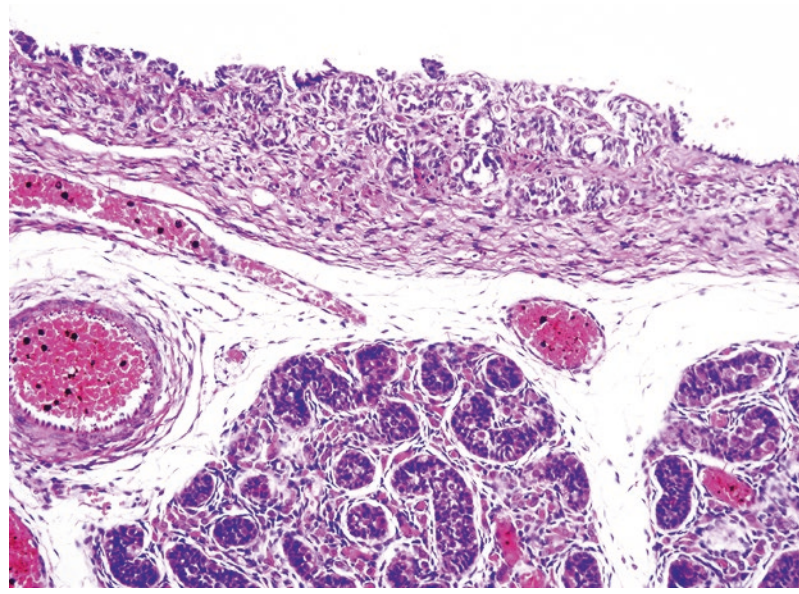

Fig. 1.4 Seminiferous tubules continue their development in the most superficial zone of the tunica respecting the deeper more cellular area and the vasculosa tunic

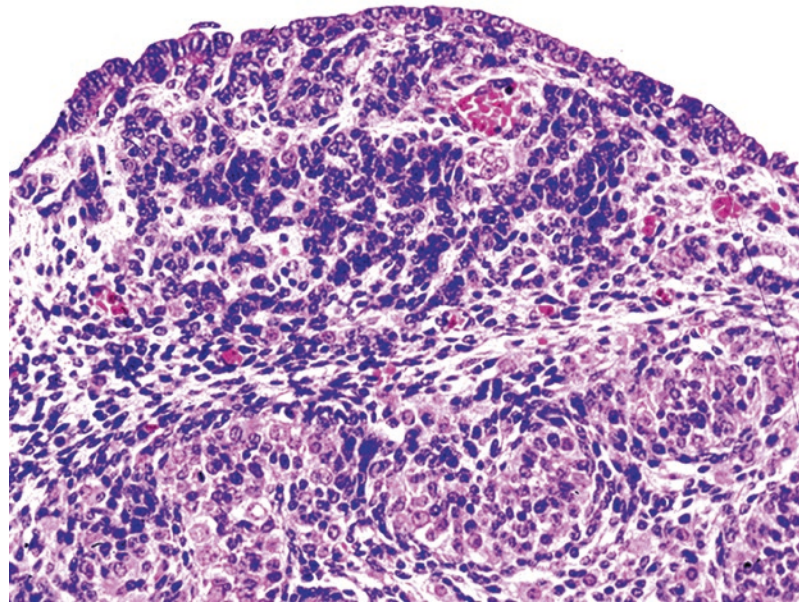

Fig. 1.5 Tunica albuginea is replaced by cell cords that appear connected with the epithelial lining. In depth there is a good delimitation with the seminiferous tubules

cords, still retain calretinin positive expression that the mesothelium used to have and show an important coexpression of inhibin in Sertoli cells. Germ cells are identified as gonocytes (positive for PLAP and OCT3/4).

Differential Diagnosis The differential diagnosis of persistent seminiferous tubules in formation in the normal tunica as well as in the persistence of testicular blastema arises with the UGT and has already been discussed in previous paragraphs. This lesion is interpreted as a late tubular neoformation, uncoupled in time, which starts after the collagenization of the tunica occurred by the action of AMH. And therefore there is a perfect demarcation between the tunica and normal testicular parenchyma. In the newborn child, it coincides with a delay in the matu-

ration of germ cells with persistently high number of gonocytes in the lumen of the seminiferous tubules of the remaining testis. Both findings are characteristic of trisomy 18.

1.4 Ectopia of Testicular Parenchyma in the Normal Tunica Albuginea

It is a focal lesion, generally single, in which the testicular parenchyma extends through the entire thickness of a histologically normal tunica. The presence of testicular parenchyma in the thickness of the tunica is rarely observed; in 0.8 % of pediatric and 0.3 % of adult autopsies, it is probably related to the number of slices studied [15]. It is more common in undescended testes than in normal testes and can be bilateral. It is not associated with DSD.

Histopathology Grossly, this lesion has been reported in the child as rounded macules on the surface of the testicle [16]. In the adult, it is described as a bunch of grapes emerging through a thin tunica albuginea of several millimeters in diameter [17]. But in most cases, it is an incidental histological finding.

The seminiferous tubules have a degree of development similar to the rest of the testicular parenchyma, and among the seminiferous tubules, there are Leydig cells in cases of newborn and in adult testes (Fig. 1.6). Ectopic tubules in adult testes can show spermatogenesis, hyalinization, or cystic transformation (Fig. 1.7). The ectopic seminiferous tubules may or may not be connected to the seminiferous tubules of the testicular parenchyma [4].

The origin of ectopic testicular parenchyma is speculative. It is a process that probably happens between gestation days 44–48, when the sexual cords are formed, and days 48–60, when the tunica albuginea is formed [18]. A delay in growth and maturation of the sex cords would cause them to get trapped inside the tunica albuginea in formation.

Differential Diagnosis The most important differential diagnosis has to be done with the gonad known as dysgenetic testis, the typical gonad of patients with male undermasculinization and Müllerian remnants. The three most important

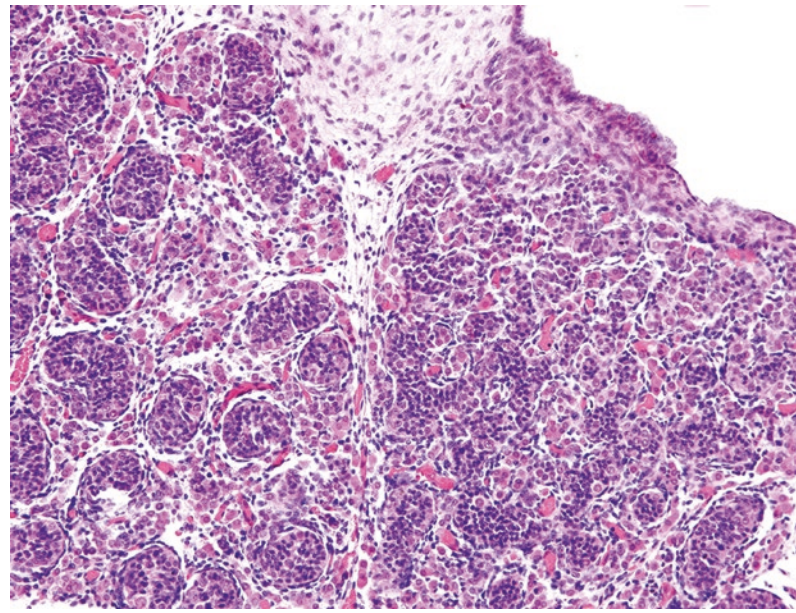

Fig. 1.6 Ectopia testicular parenchyma in the tunica albuginea of a newborn baby. The tunica albuginea is very thickened and contains testicular parenchyma formed by cell cords, seminiferous tubules, and abundant Leydig cells in the interstitium

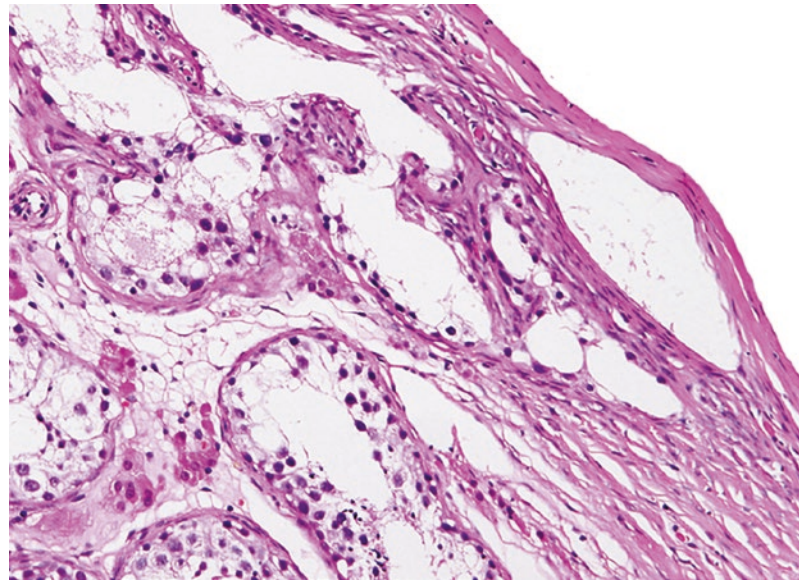

Fig. 1.7 Ectopia of seminiferous tubules present in the thickness of normal tunica albuginea in adult testis. Ectopic tubules show cystic transformation and partially preserved spermatogenesis

criteria are a tunica that is normal in thickness and collagenization, absence of a similar ovarian stroma, and clear delineation between the normal tunica albuginea and testicular parenchyma. In the adult testicles when the seminiferous tubules have undergone a cystic transformation, albuginea cysts must be discarded. These cysts sometimes are mesothelial, and other mesonephric remnants are easily identifiable by immunohistochemical techniques, positive for D2–40 and calretinin in the first case and CD10 in the second one.

1.5 Ectopia of Seminiferous Tubules in an Ovarian-Like Stroma

Testes with this lesion show two distinct areas consisting of a well-developed central testicular parenchyma and another peripheral one in which the tubular density is lower, and the stroma is similar to the ovarian stroma. Both areas may be separated by a loose connective tissue. These gonads are known as dysgenetic testis.

The albuginea is generally thick and lacks the structure and organization characteristic of the tunica of a normal testis. Cells and fibers are not parallel to the surface layers but are arranged in a swirling pattern. The tunica is not well defined from the testicular parenchyma.

The seminiferous tubules of the testicular peripheral area often show anastomosis and penetrate deep into the tunica albuginea, even reaching its surface (Fig. 1.8). Germ cells are rare, and some intratubular eosinophilic bodies and microliths can be observed [4].

Testes with these lesions are associated with the presence of Müllerian structures. The defect in the development of this albuginea is interpreted as the result of a defect in the synthesis or action of AMH, and it is the most common finding in one or both testicles that enables the pathologist to suggest that the patient has one of the following clinical syndromes: dysgenetic male pseudohermaphroditism, mixed gonadal dysgenesis (Sohval syndrome or asymmetric gonadal differentiation), and persistent Müllerian duct syndrome (male with uterus) [19] (see Chap. 4).

Patients with this type of ectopia of the seminiferous tubules require monitoring due to the high proportion of germ cell tumors that develop in the adult [20].

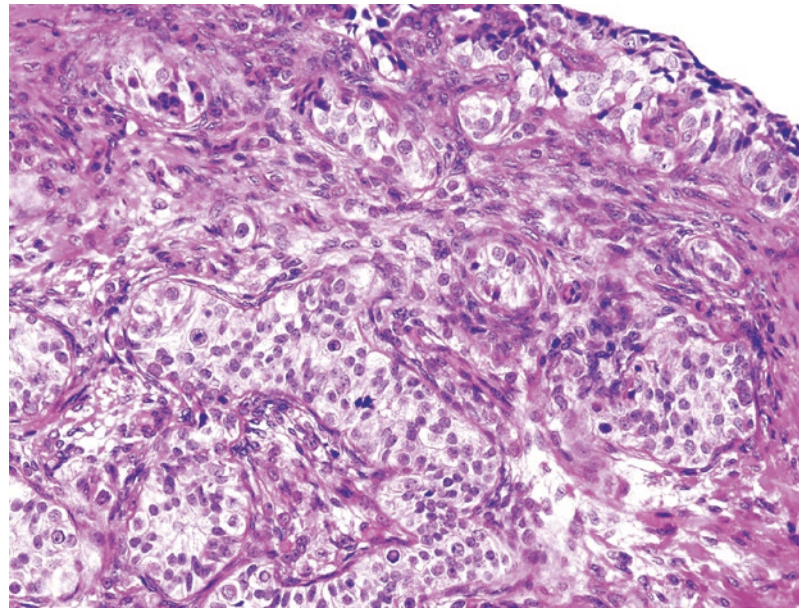

Fig. 1.8 Ectopia of seminiferous tubules present in the thickness of the tunica albuginea with ovarian-like stroma in the testis of a patient with defective AMH

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Disorders of Sexual Development from the Pathologist's Perspective

2

Manuel Nistal, Pilar González-Peramato, and Álvaro Serrano

2.1 Introduction

Disorders of sexual development (DSD) [1] are defined as those congenital conditions in which the development of chromosomal, gonadal, and anatomical sex is atypical [2]. Their frequency is estimated at 1 in 4.500–5.500 of the global population [3], but if we include all congenital genital anomalies, including cryptorchidism and hypospadias, it rises to 1:200–1:300 [4]. To solve such important issues as gender assignment, genital surgery, functional outcome, lifelong care, and psychosexual adjustments, DSD requires to be approached from different points of view such as genetic, endocrinological, histological, and surgical [5, 6]. Until just over 10 years ago, diagnoses such as hermaphroditism, pseudohermaphroditism, or intersex still persisted in literature. The consensus classification issued by the Chicago Meeting in 2005 [2] had the good sense to consider these terms obsolete and reunite all of them under the term "disorders of sexual development." It also introduced a classification based on the karyotype, as it was not possible to make a classification based on the underlying genetic error (Fig. 2.1). And certainly, it was most important to create a way of working that allows to standardize the information in order to determine the therapeutic behavior that such a varied pathology produces [7]. In itself, the classification based on the karyotype does not represent a real advance in the knowledge of the DSD for two reasons: (a) the same karyotype may result in different phenotypes with different biological behaviors and the possibility of different tumor development, and (b) very often patients are not 46,XX DSD or 46,XY DSD but have more than one cell line or a complex chromosomal constitution. Other patients as ovotesticular DSD are considered within any of the groups as the karyotype, among others, can be 46,XX, 46,XY, or 46,XY/46,XY (Fig. 2.1).

Not least important is the problem that arises when we have to explain the DSD as pathologists. There is no logical reason to use the karyotype as a starting point as the gonads grouped under the same karyotype have little histological similarities. Therefore, it is imperative to present a more didactic classification. A classification based on histology has many advantages as it allows to know the gonad leading to different genotypes, to assess its functional capacity, and to evaluate the risk of developing a germ cell tumor.

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Sex chromosome DSD	46,XY DSD		46,XX DSD		
	Disorders of testicular development	Disorders of androgen synthesis / action	Disorders of ovarian development	Fetal androgen excess	
				CAH	Non CAH
- 45,X Turner and variants - 47,XXY Klinefelter and variants - 45,X/46,XY MGD - Chromosomal ovotesticular DSD	- Complete gonadal dysgenesis - Partial gonadal dysgenesis - Gonadal regression - Ovotesticular DSD	- Androgen synthesis defect - LH-receptor defect - Androgen insensitivity - 5α–reductase deficiency - Disorders AMH - Timing defect - Endocrine disrupters - Cloacal extrophy	- Ovotesticular DSD - Testicular DSD - Gonadal dysgenesis	- 21-OH-deficiency - 11-OH deficiency	- Aromatase deficiency - POR gene defect - Maternal luteoma - Iatrogenic

DSD: Disorders of sex development, MGD: Mixed Gonadal Dysgenesis, AMH: anti-Müllerian hormone, CAH: Congenital adrenal hyperplasia

Fig. 2.1 Classification based on the karyotype of DSD

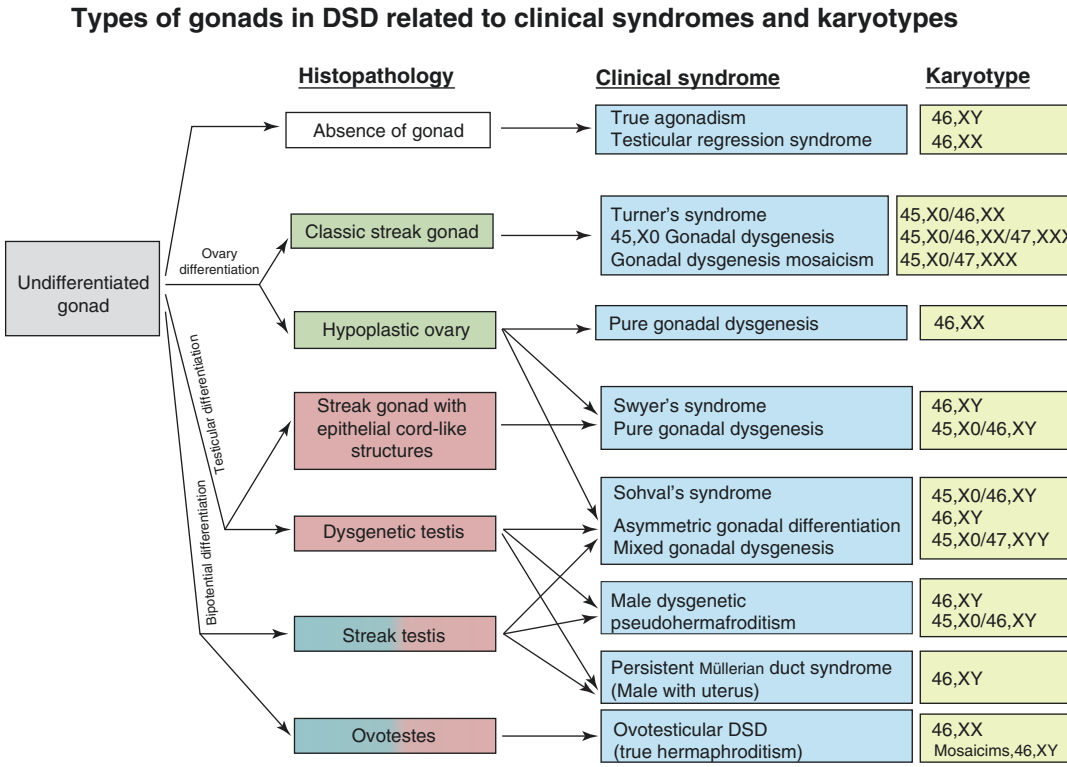

Fig. 2.2 The different types of gonads observed in DSD, the most frequent clinical patterns, and the characteristic karyotypes are shown in the figure. The structurally normal testis present in some DSD such as fetal androgen excess insensitivity syndromes, a 5-alpha-reductase defect is not included in this scheme

2.2 Histological Classification

The DSD show gonads whose structure is in different stages of development or suffer the consequence of a failure of the hormones they should have produced. When the gonad starts to differentiate into ovaries, it may develop as a streak gonad with or without ovarian follicles or become a hypoplastic ovary. If it differentiates into testes, it can be detained forming a structure similar to the streak gonad but with cords of epithelial-looking cells inside (streak testis with epithelial cords), or it may come to acquire a differentiation that grossly simulates a testicle but still presents major defects in its

differentiation (dysgenetic testes). If the gonad has a double differentiation into testis and ovary, an ovotestis is formed, but if it partially stops its differentiation, a streak testis results. If the undifferentiated gonad undergoes involution a real agonadism occurs [8–10]. Figure 2.2 shows the different types of gonads observed in DSD, the most frequent clinical patterns, and the characteristic karyotypes.

2.3 Types of Gonads

Undifferentiated Gonadal Tissue (UGT) It is characterized by the presence of germ cells which are similar to gonocytes mixed with smaller cells with hyperchromatic nucleus. There is no cordonal, tubular, or follicular formation. The immunophenotype of the germ cell is similar to that described in the gonads known as streak gonad with epithelial cords. Companion cells have Sertoli/granulosa cell characteristics. UGT is observed not only in this type of streak gonad but also in dysgenetic testis, streak testis, or ovotestis. Gonads with UGT are at high risk of gonadoblastoma and other germ cell tumor development [11].

Classical Streak Gonad A streak gonad is elongated and whitish. It consists of connective tissue that is arranged in bundles reminiscent of ovarian stroma. It is the characteristic gonad of 45,XO gonadal dysgenesia or Turner's syndrome (Fig. 2.3). The streak gonads of some of these patients contain primordial follicles, primary follicles, atretic follicles, small cysts, and clusters of hilar cells in adults (Fig. 2.4). These gonads are characteristic of Turner's syndrome with chromosomal mosaicism and of 46,XX pure gonadal dysgenesis patients (Figs. 2.5 and 2.6).

Hypoplastic Ovary The gonads are ovoid shaped, whitish, and have a smooth surface. Histologically, they show isolated primordial follicles, some primary follicles, and sometimes developing follicles. It is the characteristic gonad of 46,XX pure gonadal dysgenesis and also can be observed in some patients with ovotesticular DSD.

Streak Gonad with Epithelial Cord-Like Structures Macroscopically these gonads resemble the classical streak gonads, but their histological structure is completely different. Instead of isolated follicles, cellular cords are observed in an ovarian-like stroma. These cords do not have a specific spatial orientation, but they are anastomosing and branching. Their thickness is very variable. Histologically, they are formed by two cell types, pre-Sertoli cells and germ cells. The pre-Sertoli cells are the most numerous and notable for their small and hyperchromatic nucleus. They are supported by a basal membrane of varying thickness.

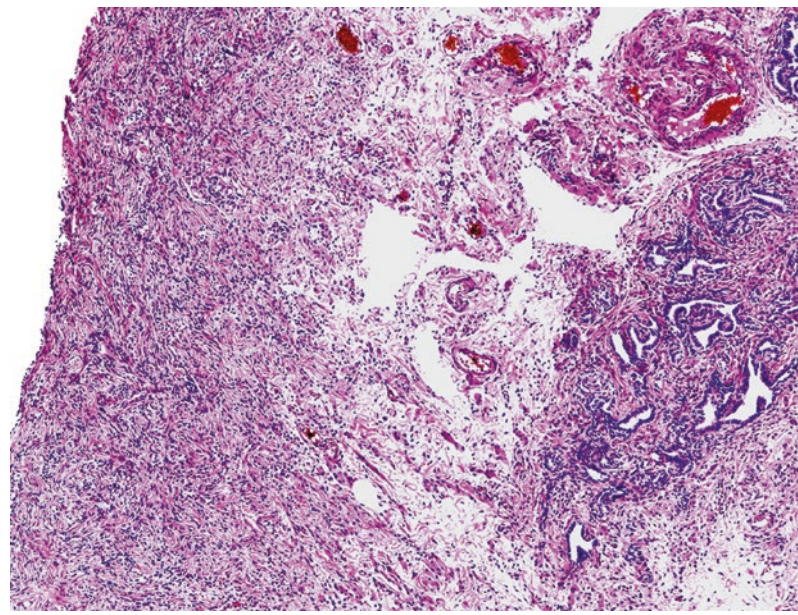

Fig. 2.3 Classical streak gonad in a patient with Turner's syndrome and karyotype 45,X0. The outer area shows a connective tissue reminiscent of ovarian stroma. Deeply, the glandular-like formations correspond to the rete ovarii

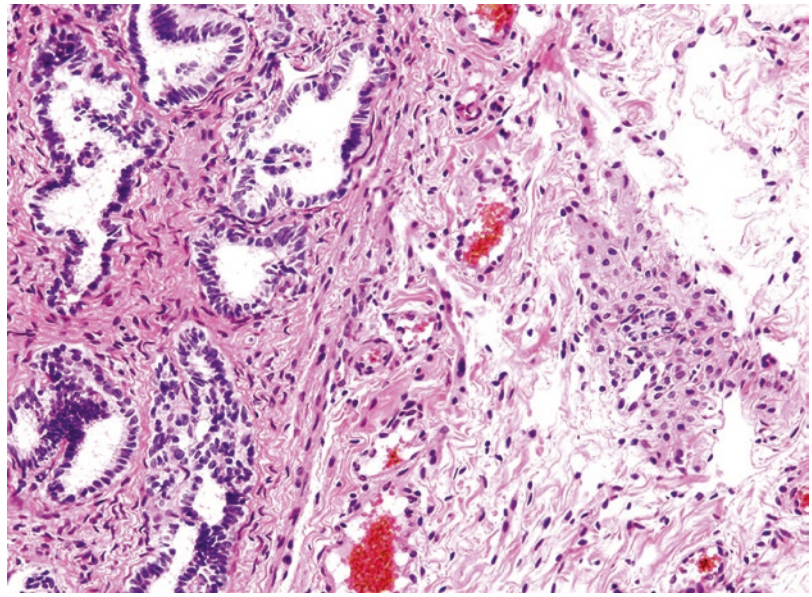

Fig. 2.4 Classical streak gonad. Beside the rete ovarii cavities, there is a cluster of hilar cells surrounding a vessel

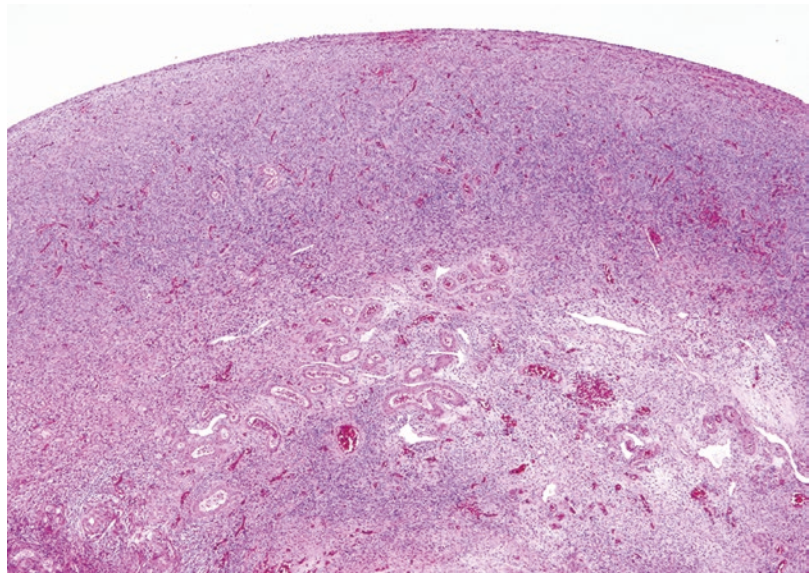

Fig. 2.5 Classical streak gonad in a 46,XX pure gonadal dysgenesis patient

Germ cells resemble gonocytes. They are located inside the epithelial cords or isolated in the stroma and have a large, vesicular nucleus, a central nucleolus, and a pale cytoplasm. Epithelial cells are strongly positive for cytokeratins AE1/AE3, moderately positive for inhibin and D2–40, and weak to AMH. The immunophenotype of germ cells is as follows: OCT3/4 +, c-Kit +, PLAP +, TSPY + (testis-specific protein Y-encoded), and VASA +. It is the characteristic gonad of 46,XY pure gonadal dysgenesis or Swyer syndrome.

Dysgenetic Testis They are small testes formed by a solid tubular grouping in the center of the gonad and a peripheral area in which the tubules are scarce and separated by an abundant stroma. The tunica albuginea is poorly collagenized, and the border with the testicular parenchyma is not well delimited. Its structure recalls the ovarian cortex. The seminiferous tubules of the peripheral zone are often anastomosed and extend through the tunica albuginea until contacting the surface. Sertoli cells of the peripheral tubules express calretinin plus inhibin and AMH. The