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Paratesticular Extramedullary Hematopoiesis in Children

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• ***Context.***—**Extramedullary hematopoiesis (EMH) is an uncommon occurrence, usually associated with hematologic disorders, but it rarely presents as an isolated finding.**

Objective.—**To determine the frequency, immunomorphologic features, and clinicopathologic background of EMH in orchiectomies from pediatric patients.**

Design.—**All orchiectomy specimens removed from children from 2008 to 2020 in our institution were retrospectively reviewed. Biopsies and neoplasias were excluded. The EMH diagnosis was rendered when hematopoietic cell precursors were present. Immunohistochemical stainings were performed to characterize the hematopoietic components.**

Results.—**Seventy-nine orchiectomies from 77 children (mean age, 5 years; range, 0–17 years) were included in our study. Forty-three patients (55.8%) underwent surgery for testicular atrophy, 30 (39.0%) for torsion, and 4 (5.2%) for intersex conditions. EMH was identified in 6 of 79 orchiectomies (7.6%), all performed for testicular torsion. All patients but one were newborns, and the remaining patient was 15 years old. No patient had evidence of a hematologic disorder. All EMH foci were in a background of reactive changes with a variable extension, either in the epididymis (4 cases) or in the deferens duct (2 cases). Immunostaining confirmed an association of myeloid (myeloperoxidase$^+$) and erythroid precursors (E-cadherin$^+$) in all 6 cases. One case also presented rare megakaryocytes, and one showed benign TdT$^+$ B-cell precursors.**

Conclusions.—**To our knowledge, this is the first study that demonstrates EMH as a common finding in orchiectomy samples, especially from newborns. Despite the lack of pathologic potential, it is important to recognize EMH in order to avoid misdiagnosis.**

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During a lifetime, hematopoietic sites progressively change. Specifically, physiological hematopoiesis begins in the yolk sac in the embryo phase, passes to the liver and spleen during the fetal second trimester, and finally transfers to the bone marrow in the fetal third trimester. As a result, the bone marrow is the primary and almost exclusive site of hematopoiesis in healthy adults, in physiological conditions.[1]

Extramedullary hematopoiesis (EMH) consists of the growth of normal hematopoietic precursor and mature cells outside the bone marrow, generally composed of 2 hematopoietic lineages, which are myeloid and erythroid cells, with inconstantly interspersed megakaryocytes.[2] Notably, EMH is an exceptional occurrence in routine pathology practice, usually related to hematologic disorders, in particular myelofibrosis, and it is typically observed in the liver, spleen, or lymph nodes. However, it has been reported in the most disparate sites of the body, including but not limited to the central nervous system, middle ear, nasopharynx, skin, breast, heart, pleural cavity, peritoneum, adrenal gland, and gastrointestinal and urinary tracts, as well as malignant and benign neoplasias.[2–6]

Following bone marrow microenvironment changes or under stressful conditions, such as anemia, infection, cancer, and metabolic impairment, many blood precursors from the bone marrow are mobilized to the periphery.[7] This phenomenon, called mobilization, is at the basis of pathologic EMH, during pathologic or exaggerated physiological processes, and it is believed to play a compensatory function for inadequate central hematopoiesis, temporarily replacing it. Nevertheless, sporadically EMH represents an isolated incidental finding, particularly in children, because prenatal hematopoiesis is by its nature extramedullary and stressful conditions can favor its endurance.

Orchiectomy is a surgical procedure of removal of the testis that is indicated for therapeutic or diagnostic purposes. In adults, the removal of the testis is more frequently performed to treat testicular or prostate cancers. Conversely, there is a range of pathologic lesions that can require orchiectomy during pediatric age, both benign and malignant. The most common lesions are benign and mainly comprise testicular torsions and atrophy, including vanishing testis.[8]

Because there are not reported searches for EMH in testicular samples, we undertook this study with the aim of determining the frequency, immunomorphologic characteristics, and clinicopathologic background of EMH in orchi-

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Table 1. Primary Antibodies and Conditions Used in This Study

Antibody	Clone	Vendor	Dilution	pH	Incubation Time, min	Stained Cells
CD10	56C6	DAKO	Prediluted	9	20	Immature lymphoid precursor Mature granulocytes
CD20	L26	DAKO	Prediluted	6.1	20	B-cell lineage
CD34	Polyclonal	DAKO	1:100	9	30	Immature precursor
CD43	DF-T1	DAKO	Prediluted	9	45	Pluripotent hematopoietic progenitor T cells
CD45	2B11+PD7/26	DAKO	Prediluted	9	15	Lymphoid lineage Maturing myeloid cells
CD61	Y2/51	DAKO	1:50	6.1	30	Megakaryocyte
CD68PGM	PG-M1	DAKO	Prediluted	9	25	Myelomonocyte lineage
CD117	QBEnd 10	DAKO	Prediluted	9	12	Immature precursor Mast cells Early erythroid precursors
E-cadherin	NHC-38	DAKO	1:50	9	25	Erythroid lineage
Glycophorin A	JC159	DAKO	1:400	9	30	Erythroid lineage
Ki-67	MIB-1	DAKO	Prediluted	6.1	20	Proliferative
Myeloperoxidase	Polyclonal	DAKO	Prediluted	9	20	Granulocyte lineage
PAX5	DAK-Pax5	DAKO	Prediluted	9	15	B-cell lineage
TdT	EP266	DAKO	Prediluted	9	15	Immature lymphoid precursor

ectomies from patients of pediatric ages. Moreover, we will discuss the spectrum of possible differential diagnoses.

MATERIALS AND METHODS

Study Cases and Clinicopathologic Data

This is a retrospective observational study conducted in the department of pathology. All experimental data were generated in accordance with the ethical standards outlined by the Helsinki Declaration.[9]

All orchiectomy specimens removed from pediatric patients (<18 years of age) from January 2008 through December 2020 in our institution, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Milan, Italy), were retrieved from the surgical pathology electronic database. Testicular biopsies and surgical specimens obtained in cases of neoplasia were not included. All available hematoxylin-eosin–stained and immunostained sections were retrospectively reviewed.

Clinicopathologic data, including patient age, surgical indication, and final pathologic diagnosis, were collected from the pathology reports. Personal clinical history, including signs, symptoms, and surgical indication, were collected from medical records, such as from the hematologic disorder medical history. The diagnosis of EMH was given when immature hematopoietic cell clusters were present. In positive cases, EMH foci were further classified according to the amount of EMH (single/multiple foci, number of cells/foci), their hematopoietic components (erythroid, myeloid, or trilineage), side, laterality, and pathologic background.

Immunohistochemical Stainings

Immunostainings were performed on 4-μm-thick sections from formalin-fixed, paraffin-embedded blocks in selected cases, using an automated immunostainer (DAKO Omnis, Agilent, Santa Clara, California). The primary antibodies used and conditions are reported in Table 1.

In brief, the sections were deparaffinized in xylene, rehydrated in graded ethanol, and incubated in distilled water. Antigen retrieval was carried out by incubating the slides in Tris/EDTA (pH9; GV800, DAKO) or citrate buffer (pH 6.1; GV805, DAKO), prior to the application of primary antibody.

Soon after, the sections were incubated in EnVision FLEX Peroxidase Blocking Reagent (GV800, DAKO) for 3 minutes to block endogenous peroxidase activity, prior to the application of primary antibody. After a signal amplification with a mouse or rabbit linker (GV821 or GV809, respectively, DAKO), the horseradish peroxidase/diaminobenzidine–based revelation systems kit (GV800, DAKO) was applied to reveal antibody binding. The slides were counterstained with hematoxylin for 5 minutes (GC808, DAKO) and dehydrated in graded ethanol and xylene. For each antibody, a positive control slide and a negative control slide, where the primary antibody was replaced with normal serum or isotype-matched antibodies, were included in every staining batch.

Statistical Analyses

The associations between categorical variables and EMH were assessed by applying the χ^2 test (or Fisher exact test, when appropriate) to estimate the P value. A P value $< .05$ was considered as statistically significant and all tests were 2-sided. All statistical analyses were conducted using GraphPad Prism 5 software (GraphPad Software, Inc).

RESULTS

Clinicopathologic Features

A total of 79 orchiectomies for benign pathologies were performed in 77 pediatric patients in the period 2008–2020 at our institution. Patient ages ranged from 0 to 17 years (mean age, 5.4 years). Of the 77 study patients, 42 (54.5%) had left-sided orchiectomy, 30 (39.0%) right-sided orchiectomy, 2 (2.6%) bilateral orchiectomy, and for the remaining 3 patients (3.9%) the laterality was not available. Among them, 43 patients (55.8%) underwent surgery for testicular atrophy, 30 (39.0%) for testicular torsion, and 4 (5.2%) showed intersex conditions. EMH was identified in 6 of 79 orchiectomies (7.6%). Clinicopathologic features of these 6 cases are summarized in Table 2. All 6 patients were operated on for testicular torsion (χ^2 test, $P = .006$); 4 of them were right sided and 2 left sided. Similar macroscopic features were found in all cases, with enlarged testis, bluish tunica albuginea, and hemorrhagic cut section, as well as marked congestion and hemorrhage of the testicular appendages.

All patients but one were newborns, and the remaining patient was 15 years old. All 5 EMH^+ newborns were born at

Table 2. Clinicopathologic Features of Pediatric Patients With Paratesticular Extramedullary Hematopoiesis

Case No.	Age	Laterality	Symptoms and Signs	US	Foci	Cell No./ Foci	Side	E-cad, %	MPO, %	TdT, %	Ki-67, %
1	2 d	Left	Perinatal left hard, swollen scrotum and hard testis	Scarce ECD vascularization left testis, dishomogeneous echostructure	Single	<100	Deferens	20	80	0	30
2	15 y	Right	Right hard, discolored, swollen scrotum and hard, painful testis	No vascular ECD signs right testis, dishomogeneous echostructure	Few	<100	Deferens	40	60	NA	NA
3	1 d	Right	Perinatal right hard, discolored, swollen scrotum and hard testis	No vascular ECD signs right testis, dishomogeneous echostructure	Multiple	<100	Epididymis	30	70	0	40
4	1 d	Right	Perinatal right hard, discolored, swollen scrotum and hard testis	Scarce vascular ECD signs right testis, dishomogeneous echostructure	Multiple	<50	Epididymis	60	40	0	70
5	6 d	Right	Right hard discolored, swollen scrotum and hard testis	Scarce vascular ECD signs right testis, dishomogeneous echostructure	Multiple	<20	Epididymis	Rare	70	40	60
6	1 d	Left	Perinatal left hard, discolored, swollen scrotum and hard testis	No ECD vascularization left testis	Multiple	>100	Epididymis	80	10	0	95

Abbreviations: E-cad, E-cadherin; ECD, echo-color Doppler; MPO, myeloperoxidase; NA, not available; US, ultrasonography.

full term. Globally, EMH was found preferentially in newborns, 5 of 14 (35.7%) who underwent orchiectomy in our institution, as compared with other ages (Fisher exact test, $P = .001$). There was no evidence of preexisting or subsequent hematologic disorder in any of the cases, and complete blood counts were normal in all cases.

In 4 cases EMH foci were in the connective tissue of the epididymis, often with cuffing distribution, and in 2 cases in the stroma of the deferens duct. All EMH foci were in a background of reactive changes associated with massive testicular necrosis, with or without necrotic epididymis (in 4 cases), containing diffuse extravasated erythrocytes, dispersed fibrin, scattered macrophages (often hemosiderin laden), and hemosiderin deposition. In all cases, EMH was incidental and microscopic, with a variable extension of EMH foci, ranging from a few clusters of about 20 cells up to many clusters of hundreds of cells in one case (case 6). At histopathologic examination, EMH foci were composed of mixed populations of hematopoietic precursor cells, recognizable for their specific morphologic features, in variable proportions (Figure 1, A and B). Myeloid precursor cells had midsized indented nuclei, small nucleoli, and moderately abundant granular eosinophilic cytoplasm. On the other hand, erythroid precursors showed jet-black round nuclei and eosinophilic cytoplasm. Specifically, the myeloid and erythroid lineages were prevalent, and very rare conclusive megakaryocytes were identified in only one case (case 6).

Immunohistochemical Profile

Immunohistochemical staining confirmed the presence of hematopoietic precursors in all 6 cases. Most EMH foci showed immunohistochemistry positivity for CD43, a marker of pluripotent hematopoietic progenitors.[10] Importantly, an association between both myeloid and erythroid precursors was revealed by positivity for myeloperoxidase and E-cadherin/glycophorin A, respectively (Figure 2, A through E). There were various proportions of the different hematopoietic cell lineages; in 4 cases the myeloid precursors were prevalent (cases 1, 2, 3, and 5), whereas in the other 2 cases the erythroid precursors were dominant (cases 4 and 6) (Table 2). In the case with morphologic evidence of megakaryocytes, they were highlighted by CD61

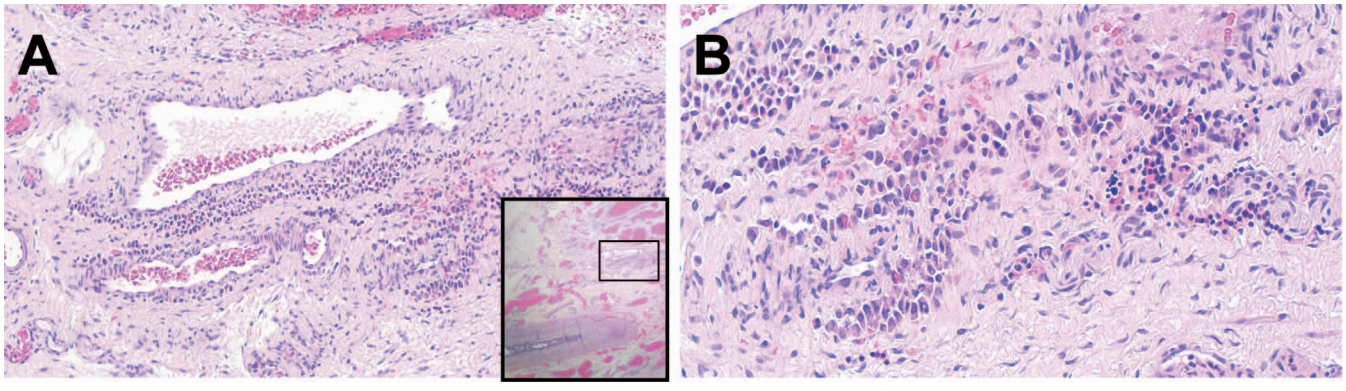

Figure 1. *In case 1, in the context of a congested deferens duct, perivascular cuffing of blue cells is appreciable (A). At higher magnification, the cell clusters are composed mainly of immature myeloid precursors with a minor component of erythroblasts (B) (hematoxylin-eosin, original magnifications ×40 [A inset], ×100 [A], and ×200 [B]).*

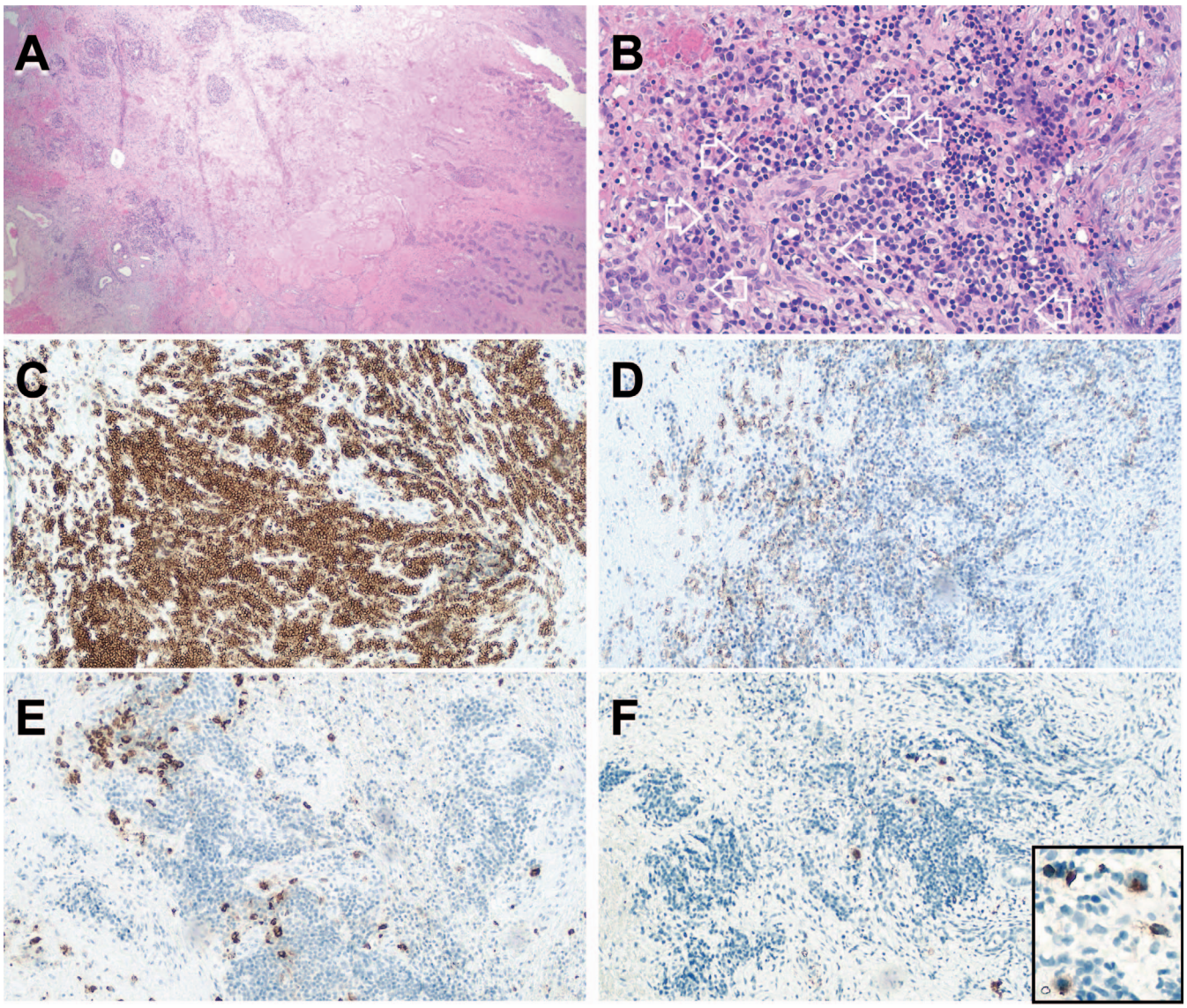

Figure 2. *At low magnification, the testis in case 6 appears massively hemorrhagic and completely necrotic (lower right-hand corner), and the epididymis is hemorrhagic with multiple aggregates of blue cells (lower left-hand corner) (A). At higher magnification, these cells have scant cytoplasm, a variable dark nucleus, and sometimes 1 or 2 inconspicuous nucleoli, and they display many mitotic figures (arrows) (B). The majority of these cells are positive for glycophorin A (C) and express E-cadherin (D), being erythroid precursor cells. Moreover, admixed myeloid precursors (about 10%) are highlighted by myeloperoxidase (E), and rare megakaryocytes are identified by CD61 (F). Indeed, higher magnification shows CD61-stained cells morphologically consistent with megakaryocytes (inset in F) (hematoxylin-eosin, original magnifications ×20 [A] and ×200 [B]; original magnifications ×100 [C through F] and ×400 [F inset]).*

immunostaining (Figure 2, F). Interestingly, only one case showed TdT-positive cells compatible with B-cell precursors (case 5). To better characterize these cells, case 5 was further stained with PAX5, CD20, and CD10, showing expression of PAX5 and weak positivity for CD10, thus more consistent with hematogones (Figure 3, A through D). Moreover, this case was the only one with a diffuse immunopositivity for CD45, as opposed to the other 4 evaluated cases, in which only a minority of EMH cells demonstrated CD45 expression. In all cases, immunostainings for CD68 and CD117 showed sparse positive macrophages and mast cells, respectively, whereas CD34 was constantly negative in all hematopoietic cells. In only one case (case 3), CD117 stained a minority (10%) of immature myeloid cells in EMH foci. In all evaluated EMH cases, hematologic precursors had a high Ki-67 proliferation index, 30% or higher, with a median value of 60%.

DISCUSSION

Even though extremely rare, EMH has been reported in the literature in many parts of the human body, in addition to the favored sites spleen, liver, and lymph nodes.[11] Nevertheless, to our knowledge, this is the first study that demonstrates EMH as a common, incidental finding in orchiectomy samples, especially from newborns, where in more than one-third of the patients it was identified. In all cases, paratesticular EMH was identified in the setting of testicular torsion.

Under normal circumstances, throughout the third fetal trimester, hematopoietic precursors shift from the liver and

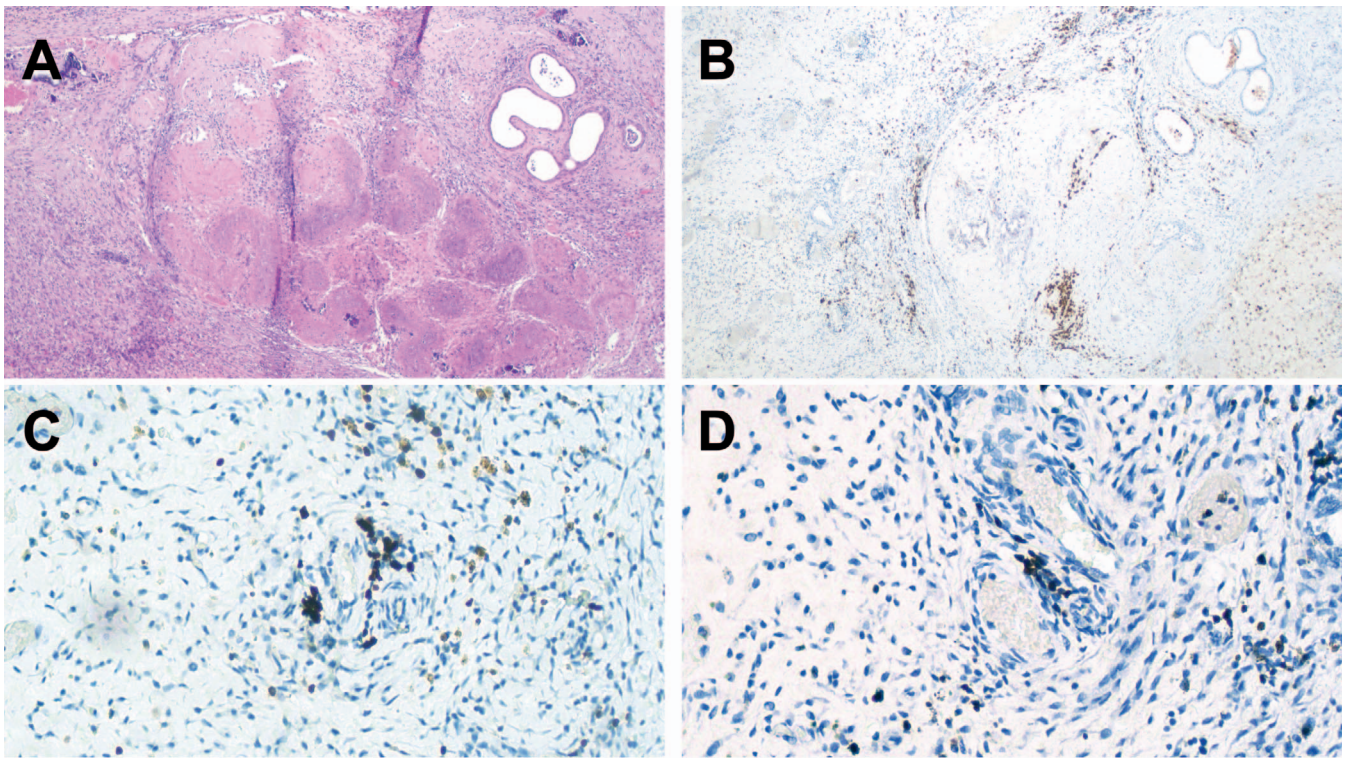

Figure 3. *At low magnification, in case 5 the epididymis appears massively necrotic with focal calcifications and some aggregates of small blue cells (A). Myeloperoxidase (MPO) stains many of the foci of extramedullary hematopoiesis (B). At higher magnification, a minority of these MPO$^+$ cells were also positive for TdT (C) and PAX5, so most consistent with hematogones (D) (hematoxylin-eosin, original magnification ×40 [A]; original magnifications ×100 [B] and ×200 [C and D]).*

spleen to dwell definitely in the bone marrow for the rest of life, and EMH occurs only rarely.[1] Although the pathophysiological mechanisms of EMH are not completely understood, 4 main theories have emerged to explain the causes.[7,12] First, bone marrow failure could favor the mobilization of hematopoietic precursors and the colonization of other tissues, such as in hematologic disorders.[13] Second, the myelostimulation, in which an overstimulation of the hematopoiesis in the bone marrow results in concurrent reactivation of fetal hematopoietic niches.[14] Third, tissue injury, inflammation, and repair may induce local EMH by aberrant production of inflammatory cytokines through recruitment of bone marrow cells.[4,15] Fourth, the local or systemic abnormal production of cytokines may stimulate stem cells to differentiate into hematopoietic cells. Interestingly, it is plausible that more factors may contribute to the onset of EMH.

The pathogenesis of EMH in paratesticular tissues has never been investigated. EMH being found mainly in newborns, we believe that the presence of fetal physiological EMH may somehow also favor hematopoiesis in other, undesignated sites, such as inflamed testis. Moreover, it is the inflammation background found in testicular torsion, similarly to myocardial infarct, that could induce EMH in response to tissue repair–associated cytokines, and not the ischemia itself.[4,15]

Occasionally, the histologic finding of EMH can raise diagnostic challenges, particularly when substantial and seen in unexpected sites. Among our EMH cases, one (case 6) showed many foci of EMH composed of hundreds of small blue round cells (Figure 2, A and B), mitotically very active, with a Ki-67 proliferation index of 95%, which was initially considered suspicious for malignancy.[3,16–18] The differential diagnosis of paratesticular EMH in a newborn includes lymphoma, leukemia, and germ cell tumors, particularly yolk sac tumor, but also small round cell tumors common in children, particularly rhabdomyosarcoma, neuroblastoma, and nephroblastoma (Wilms tumor), which can metastasize to the testis from a primary kidney cancer, but can also arise in paratesticular structures.

Lymphoma and leukemia in the testis are rare, accounting for 2% to 5% of all pediatric tumors, usually secondary to the spread of systemic acute lymphocytic or myelogenous leukemia,[19] or primary follicular and B-lymphoblastic lymphomas. In our series of patients, the identification of clusters of myeloid precursors in the paratesticular tissue raised the question of a differential diagnosis with myeloid sarcoma. In this context, the absence of a significant blast population together with the documentation of a bilineage or trilineage hematopoiesis and the exclusion of concurrent hematologic abnormalities suggests the correct diagnosis. Moreover, in case 5, the identification of TdT$^+$ B cells requires a differential diagnosis with a B-lymphoblastic leukemia/lymphoma. The absence of significant clustering of the TdT$^+$ cells, together with a morphologic variability in size and the absence of hematologic abnormalities, allows the correct diagnosis.

The yolk sac tumor is the most common germ cell tumor in prepuberal age. Usually, it forms a testicular solid nodule, composed of polygonal cells with eosinophilic secretions or clear cell cytoplasm, often showing areas of brisk mitotic activity, but rarely the cells have dense nuclei and scant cytoplasm, looking like blastema. In its solid pattern, the yolk sac tumor may morphologically resemble EMH;

however, its gross appearance, location, and immunohistochemical expression for low-weight cytokeratin, SALL4, glypican-3, and AFP distinguish this tumor from EMH.

The main tumor that should be ruled out in case of significant paratesticular EMH is rhabdomyosarcoma, which represents the most common paratesticular tumor in children.[20] Usually, patients have a hard, painless scrotal mass with heterogeneous echogenicity. Nearly all paratesticular rhabdomyosarcoma are of embryonal subtype, therefore composed of small undifferentiated blue round cells with scant cytoplasm and dispersed rhabdomyoblasts, which typically show immunohistochemical expression of myogenin, MyoD1, desmin, and actin. Also, Wilms tumor can be composed of small blastematous cells, but they immunohistochemically express WT1 and CD56.

This study, although limited by the small number of cases, has shown for the first time the presence of EMH foci in a relevant proportion of orchiectomy samples in children. Notably, in this setting, EMH most likely represents an epiphenomenon linked to the local inflammatory status rather than a pathologic process or expression of underlying hematologic disorders. Regardless, despite the lack of pathologic potential, the pathologist must be aware of the possible presence of EMH foci in this unexpected site to be able to recognize them and avoid misdiagnosis.

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