Henry Ford Health
Henry Ford Health Scholarly Commons

Pathology and Laboratory Medicine Articles | Pathology and Laboratory Medicine

1-1-2021

Hepatoid Teratoma, Hepatoid Yolk Sac Tumor, and Hepatocellular Carcinoma: A Morphologic and Immunohistochemical Study of 30 Cases

Khaleel I. Al-Obaidy

Sean R. Williamson
Henry Ford Health, SWILLI25@hfhs.org

Nathan Shelman

Muhammad T. Idrees

Thomas M. Ulbright

Follow this and additional works at: https://scholarlycommons.henryford.com/pathology_articles

Recommended Citation
Al-Obaidy KI, Williamson SR, Shelman N, Idrees MT, and Ulbright TM. Hepatoid Teratoma, Hepatoid Yolk Sac Tumor, and Hepatocellular Carcinoma: A Morphologic and Immunohistochemical Study of 30 Cases. Am J Surg Pathol 2021; 45(1):127-136.

This Article is brought to you for free and open access by the Pathology and Laboratory Medicine at Henry Ford Health Scholarly Commons. It has been accepted for inclusion in Pathology and Laboratory Medicine Articles by an authorized administrator of Henry Ford Health Scholarly Commons.

Hepatoid Teratoma, Hepatoid Yolk Sac Tumor, and Hepatocellular Carcinoma

A Morphologic and Immunohistochemical Study of 30 Cases

Khaleel I. Al-Obaidy, MD, Sean R. Williamson, MD,† Nathan Shelman, MD,* Muhammad T. Idrees, MD,* and Thomas M. Ulbright, MD**

Abstract: Rare hepatoid teratomas (HTs) in testicular germ cell tumor patients mimic hepatoid yolk sac tumor (HYST) and hepatocellular carcinoma (HCC). We compared the features of 2 metastatic HTs, 12 HYSTs, and 16 HCCs. The mean ages were 36, 40, and 62.5 years, respectively. The HTs formed sheets of hepatocyte-like cells with macrovesicular fat arranged in vague lobules with intervening fibrous bands containing biliary ductule–like structures and abortive portal triads. HTs lacked basement membrane deposits, with hepatoid cells staining for glypican-3, arginase, and HepPar-1 (2/2), whereas stains for CK19 (2/2) and CK7 (1/2) highlighted ductules and for villin hepatoid cells and ductules (1/2). SALL4 and CDX2 stains were negative (0/2). HYSTs formed nests, trabeculae, cords, and occasional gland-like structures, and most (10/12; 83%) produced intercellular basement membrane. No Mallory-Denk bodies were seen. Stains for SALL4 (100%), glypican-3 (100%), CK19 (88%), CDX2 (88%), and villin (75%) were positive, whereas those for HepPar-1 highlighted rare tumor cells (70%) and for arginase were mostly negative (26%). All HCCs lacked basement membrane deposits, with Mallory-Denk bodies occurring in 50%. Stains for HepPar-1 (100%) and arginase (94%) were positive, glypican-3 infrequent (19%), and SALL4, CK19, villin, and CDX2 negative. In summary, HTs are distinguished from HYST by the formation of ductules and abortive portal tracts, lack of basement membrane deposits, more consistent staining for arginase and HepPar-1, and negativity for SALL4 and CDX2. Contrasting features of HCCs with HYSTs include negativity for SALL4, CK19, and CDX2, frequent Mallory-Denk bodies, and absence of basement membrane deposits.

Key Words: yolk sac tumor, hepatoid yolk sac tumor, teratoma, hepatoid teratoma, hepatocellular carcinoma, germ cell tumors

(*Am J Surg Pathol* 2021;45:127–136)

From the *Department of Pathology & Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN; and †Department of Pathology and Laboratory Medicine, Henry Ford Health System, Detroit, MI.

K.I.A. and S.R.W. contributed equally.

Conflicts of Interest and Source of Funding: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

Correspondence: Thomas M. Ulbright, MD, Department of Pathology & Laboratory Medicine, Indiana University Health Pathology Laboratory, Room 4014, 350 West 11th Street, Indianapolis, IN 46202 (e-mail: tulbrigh@iu.edu).

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

The yolk sac tumor (YST) of the testis is known for its divergent differentiation, including the formation of hepatocyte-like tumor cells, so-called hepatoid yolk sac tumor (HYST).[1] Although pure YST is a relatively common finding in primary testicular tumors of prepubertal children,[2] in older patients pure YST is most often found in metastatic sites following chemotherapy and disproportionately in late recurrences many years after initial treatment.[3,4] This circumstance is especially the case for HYST. In our practice, we discovered a potential mimicker of HYST that also occurred in metastatic sites following chemotherapy and showed striking hepatic differentiation. These tumors, however, resembled normal liver, showing sheets of hepatocyte-like cells with large fat vacuoles and the formation of biliary ductules and abortive portal structures. Consequently, we felt they were best classified as "hepatoid teratomas" (HTs). To the best of our knowledge, comparable HTs of testicular origin have not previously been reported, and their hepatic differentiation initially raised questions regarding their nature, including that they were variants of HYST, independent, well-differentiated hepatocellular carcinomas (HCCs), surgical errors, or mislabeled specimens. The presence of other teratomatous elements or foci of classic YST provided convincing evidence against all of the latter 3 possibilities, but HYST could not be excluded on that basis, and we realized that future cases may not always have an association with additional germ cell tumor elements. We, therefore, sought to compare the clinical, pathologic, and immunohistochemical features of HYST, HT, and HCC.

MATERIALS AND METHODS

Our institutional review board approved this study. An electronic search was performed of our surgical pathology databases for metastatic HYST and HT. Twelve cases of HYST and 2 cases of HT were retrieved from pathology department files and the authors' consultation archives at Indiana University and Henry Ford Health System. A control group comprised of 16 de novo HCCs was randomly selected from the pathology archives at Indiana University. All hematoxylin and eosin–stained slides were reviewed by 2 pathologists (T.M.U. and K.I.A.) to confirm the diagnosis. The HCC cases were additionally reviewed by a gastrointestinal/hepatic pathologist (N.S.).

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Sections of 4 μm thickness were stained with antibodies directed against SALL4 (6E3; BioCare Medical, Pacheco, CA), cytokeratin 7 (OV-TL 12/30; Dako, Agilent, Santa Clara, CA), cytokeratin 19 (RCK108; Dako, Agilent), CDX2 (DAK-CDX2; Dako, Agilent), glypican-3 (1G12; Cell Marque, Rocklin, CA), arginase (SP156; Dako, Agilent), HepPar-1 (OCH108; Dako, Agilent), and villin (1D2 C3; Dako, Agilent) in a Dako automated instrument. Positive and negative controls gave appropriate results for each stain. The staining extent was recorded as negative, focal (1+; <25%), intermediate (2+; 25% to 75%) or diffuse (3+; >75%), and the intensity was recorded as negative, weak (1+), moderate (2+), or strong (3+). Only slides with >90% HYSTs were selected for immunohistochemical analysis. Follow-up information and mortality data were obtained from patients' electronic records and physicians' offices.

RESULTS

Hepatoid Yolk Sac Tumor

The clinicopathologic features are summarized in Table 1. The patient cohort consisted of 12 men. The mean and median ages at the time of initial diagnosis were each 25 years (range, 17 to 39 y; initial age unknown for 1 patient). All patients had primary testicular nonseminomatous germ cell tumors that were predominantly of mixed nature. Three had metastases at presentation and 9 developed metastases later in their clinical courses. The 8 patients with available data who developed metastatic HYST after initial diagnosis and

TABLE 1. Clinicopathologic Characteristics of Cases of HYST (N = 12) and HT (N = 2)

	Case No.	Age*	Primary Diagnosis	Source of Hepatoid Specimen	Clinical Information and Management After Primary Testicular Diagnosis	Time After Presentation to Excision of Hepatoid Specimen	Outcome (Duration After initial diagnosis)
HYST	1	39	Testicular mixed germ cell tumor	RPLND	History of multiple recurrences Received multiple courses of chemotherapy	10 y	A (2 y)
	2	42	Testicular mixed germ cell tumor	RPLND	NA	NA	NA
	3	39	Testicular mixed germ cell tumor	RPLND	Multiple recurrences Received multiple courses of chemotherapy	22 y	A (3 y)
	4	25	Testicular nonseminomatous germ cell tumor	Mediastinal mass excision	Received multiple courses of chemotherapy	8 y	A (5 y)
	5	41	Testicular mixed germ cell tumor	RPLND	Multiple RPLN recurrences Received multiple courses of chemotherapy	23 y	A (2 y)
	6	30	Testicular mixed germ cell tumor	Mediastinal mass excision	Received multiple courses of chemotherapy. Presented with elevated level of AFP	2 y	A (1 y)
	7	33	Testicular mixed germ cell tumor	RPLND	Received multiple courses of chemotherapy Presented with elevated level of AFP	8 y	A (NA)
	8	39	Testicular mixed germ cell tumor	RPLN biopsy	Received multiple courses of chemotherapy	22 y	A (4 y)
	9	63	Testicular nonseminomatous germ cell tumor	Lung segmentecto-my	Received multiple courses of chemotherapy and RPLND	24 y	NA
	10	31	Testicular mixed germ cell tumor	Liver biopsy	Presented with multiple hepatic lesions Received chemotherapy after diagnosis	NA	NA
	11	20	Testicular mixed germ cell tumor	RPLND	Presented with retroperitoneal metastases Received chemotherapy after diagnosis	4 mo	NA
	12	34	Testicular mixed germ cell tumor	Mediastinal mass excision	Presented with retroperitoneal and mediastinal metastases Received chemotherapy after diagnosis	3 mo	DOD (5 y)
HT	1	36	Testicular mixed germ cell tumor	RPLND	Received chemotherapy	6 mo	A (2 y)
	2	44	Testicular mixed germ cell tumor	RPLND	History of multiple recurrences Received multiple courses of chemotherapy	5 mo	DOD (8 mo)

*At the time of resection of HYST specimen.
A indicates alive; AFP, alpha-fetoprotein; DOD, died of disease; NA, not available; RPLN, retroperitoneal lymph node; RPLND, retroperitoneal lymph node dissection.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

chemotherapy did so at a median of 16 years (range, 2 to 24 y) after presentation. The mean and median ages at the time of resection of the HYSTs were 36 and 37 years, respectively (range, 25 to 63 y). Follow-up data were available for 8 patients (range, 1 to 5 y after last surgical intervention); all were alive, except for 1 who died of disease 5 years following initial presentation.

On microscopic examination, the tumors showed differing proportions of solid, nested, corded/trabecular, and pseudoglandular patterns (Figs. 1A–D) that were variably interspersed with fibrous tissue that occasionally contained eosinophilic basement membrane deposits (Fig. 1B). The tumor cells had polygonal to columnar profiles and moderate amounts of eosinophilic to clear cytoplasm that occasionally contained large vacuoles of fat (Fig. 1B). The nuclei were round to ovoid with vesicular to granular chromatin and mostly single, prominent nucleoli (Fig. 1D). All tumors showed nuclear pleomorphism and frequent mitotic figures, often more so in solid areas, which also showed frequent foci of tumor necrosis, although necrosis also occurred in other areas. Foci of conspicuous intercellular basement membrane deposits were a distinctive feature in 10/12 (83%) tumors (Fig. 1D). No HYST formed Mallory-Denk bodies.

On immunohistochemical study (Table 2), all HYSTs (10/10) showed strong and diffuse reactivity for antibodies directed against SALL4 (Fig. 2A) and glypican-3 (Fig. 2B). Staining with at least moderate intensity and focal extent for CDX2 (Fig. 2C) (7/8, 88%) and at least weak intensity and focal extent for CK19 (Fig. 2D) (7/8, 88%) was only slightly less common. Stains for villin with at least moderate intensity and intermediate extent were also positive in most cases (6/8; 75%). They highlighted cell membranes in solid areas and luminal aspects in gland-like foci. HepPar-1 stained only a few tumor cells in a single cell distribution in 6 tumors (55%), was patchy positive in 2 (Fig. 2E) (18%), and negative in 3. Immunoreactivity for arginase was less frequent, occurring in 45% of tumors (patchy in 2 and in rare cells [< 5%] in 3) (Fig. 2F) (5/11). CK7 was uniformly negative in all tumors (0/9).

Hepatoid Teratoma

The clinicopathologic features are summarized in Table 1. The patients presented at ages 36 and 44 years with mixed germ cell tumors of the testis. Both had initial retroperitoneal lymph node metastases and were treated with multiple courses of cisplatin-based chemotherapy followed by resections of residual masses in the retroperitoneum at 6 and 5 months, respectively. On follow-up, the first patient was alive with no evidence of disease at 24 months after his initial presentation. The second patient received multiple courses of chemotherapy and stem cell transplantation, however, he died of progressive YST (see below) 8 months following the retroperitoneal lymphadenectomy.

On microscopic examination, the HTs formed sheets of hepatocyte-like cells subdivided by thick bands of fibrous stroma into a lobular arrangement (Fig. 3A). The tumor cells had abundant, eosinophilic cytoplasm, round nuclei with small nucleoli, and frequent large lipid vacuoles (Fig. 3A, inset). The fibrous bands contained occasional well (Fig. 3B) to poorly formed (Fig. 3C), biliary ductule–like structures, and hemosiderin-laden macrophages. A rare portal triad was found in 1 case (Fig. 3D). Both lacked sinusoid-like spaces lined by endothelial cells. Case 1 had associated teratomatous glial elements and case 2 showed residual foci of classic yolk sac tumor. Neither case showed intercellular basement membrane deposits or Mallory-Denk bodies.

On immunohistochemical study (Table 2, Fig. 4), both tumors were diffusely positive for glypican-3, HepPar-1, and arginase (2/2), whereas stains for CK19 (2/2) and CK7 (1/2) were restricted to ductular-like structures. Villin was positive in 1 tumor in both hepatocytes (membranous) and ductules (luminal). Both HTs were negative for SALL4 and CDX2, although the former highlighted the residual YST in case 2.

Hepatocellular Carcinoma

The clinicopathologic features are summarized in Table 3. Sixteen HCCs were included for analysis. Tumor size (largest nodule) ranged 3 to 24.5 cm, with a mean of 8.4 cm. Microscopic examination showed a mix of well-differentiated (44%), moderately differentiated (50%), and poorly differentiated (6%) neoplasms. The HCCs were arranged in trabecular and pseudoacinar patterns. Mallory-Denk bodies were seen in half (8/16), with only rare pale bodies and ground glass change. Bile pigment was often (44%) identifiable in pseudoacinar structures, and intratumoral steatosis (25%) was not uncommon. No intercellular basement membrane deposits were identified.

Immunohistochemical Analysis

The immunoreactivities are summarized in Table 2, which shows that SALL4 positivity distinguished HYST from both HT and HCC, as did reactivity for CDX2, although with diminished (88%) sensitivity. Cytokeratin 19 was also useful in this regard, with frequent (88%) reactivity in HYSTs, negativity in HCC and reactivity limited to bile ducts in HTs. Villin was less sensitive (75%) for HYST than CDX2 and also occurred in 1 of the HTs in both the hepatocytes and bile duct-like structures. The absence of arginase reactivity favored HYST over both HT and HCC, whereas negativity for glypican-3 was significantly more frequent in HCC than in either HYST or HT. We did not find HepPar-1 or cytokeratin 7 to be useful for differential diagnosis of these entities.

DISCUSSION

The discovery of a hepatoid neoplasm in a patient with a history of a germ cell tumor raises several differential diagnostic possibilities. These include HYST, hepatic differentiation of a teratoma, and an unrelated HCC. These considerations often have different prognostic and treatment implications. It is recognized that the presence of YST in metastases is associated with less favorable outcomes than other forms of nonseminomatous germ cell tumor.[5,6] In addition, the finding of any form of viable nonteratomatous germ cell tumor in post-chemotherapy resections is associated with reduced survival and implies the need for additional and often intensive chemotherapy.[7] Furthermore, persistent, viable germ cell tumor (other than teratoma) in the context of "late recurrence"

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

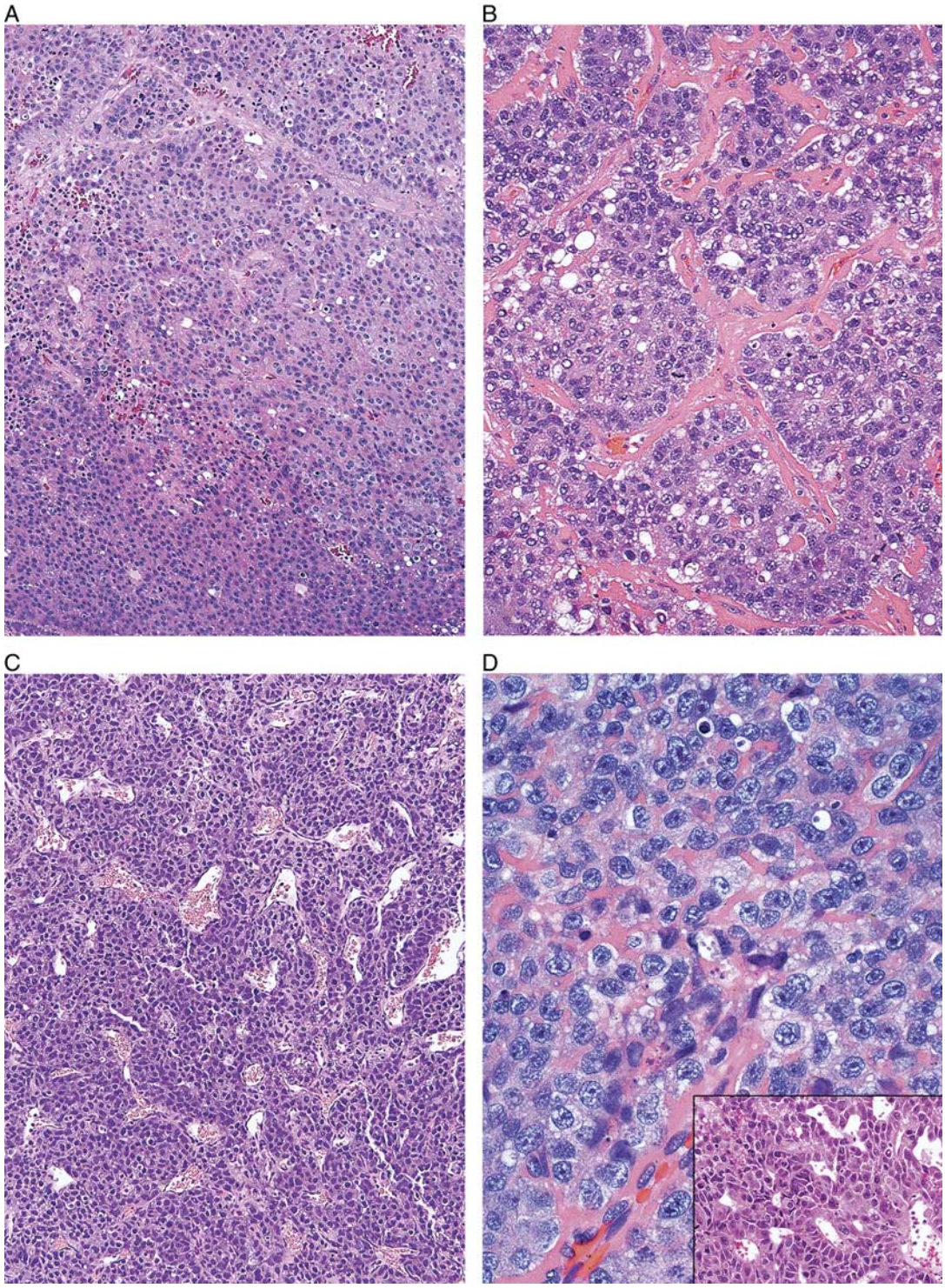

FIGURE 1. HYST showing differing proportions of solid (A), nested (B), corded/trabecular (C), and pseudoglandular (D, inset) patterns interspersed with variably thick fibrous tissue bands (B). Prominent intercellular basement membranes deposits are noted (D), as well as in perivascular areas (B). The cells have polygonal to columnar profiles and eosinophilic to pale cytoplasm with moderate nuclear pleomorphism (D).

(considered 2 or more years after initial treatment),[4] which applied to at least 8 of our cases of HYST, carries an especially poor prognosis.[4] In contrast, teratoma in postchemotherapy resections is associated with a favorable outcome and requires no additional treatment,[8] and, although there is no specific experience with HT because of its rarity, there is also no reason

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 2. Immunohistochemical Characteristics of Hepatoid Tumors

Antibody (Intensity; Extent)*	Case No.	SALL4	Glypican-3	CDX2	CK19	Villin	HepPar-1	Arginase	CK7
HYSTs	1	3+; 3+	2/3+; 3+	3+;3+	3+; 2+	2+; 2+	3+; 2+	1+; 1+	0
	2	3+; 3+	3+; 3+	NP	NP	0	3+; 1+	0	0
	3	3+; 3+	3+; 2+	3+; 2+	3+; 2+	3+; 3+	3+; 1+	0	0
	4	3+; 3+	3+; 3+	3+; 2+	3+; 2+	NP	3+; 1+	0	0
	5	3+; 3+	3+; 2+	2+; 2+	2/3+; 2+	3+; 3+	0	3+; 1+	0
	6	3+; 3+	3+; 2+	3+; 2+	3+; 1+	2+; 2+	3+; 1+	2+; 1+	0
	7	3+; 3+	3+; 3+	3+; 3+	1+; 1+	3+; 3+	3+; 2+	2+; 2+	0
	8	3+; 3+	3+; 3+	NP	NP	NP	0	0	NP
	9	NP	NP	NP	NP	NP	3+; 1+	0	NP
	10	3+; 3+	3+; 3+	0	0	0	0	0	0
	11	NP	NP	NP	NP	NP	NP	NP	NP
	12	3+; 3+	3+; 3+	3+; 1+	3+; 2+	3+; 2+	3+; 1+	2+; 2+	0
	% positive (mean intensity/extent)	100 (3+; 3+)	100 (3+; 2.7+)	88 (2.5+; 1.9+)	88 (2.3+; 1.5)	75 (2+; 1.9+)	75 (2.2+; 0.9+)	45 (0.9+; 0.6+)	0 (0; 0)
HTs	1	0	3+; 3+	0	3+; 1+†	2+; 2+	3+; 3+	3+; 3+	0
	2	0	3+; 3+	0	3+; 1+†	0	3+; 3+	3+; 3+	3+; 1+†
	% positive (mean intensity/extent)	0 (0; 0)	100 (3+; 3+)	0 (0; 0)	100 (3+; 1+)	50 (1+; 1+)	100 (3+; 3+)	100 (3+; 3+)	50 (1.5+; 0.5+)
HCCs	% positive (mean intensity/extent) N = 16	0 (0; 0)	19 (0.3+; 0.6+)	0 (0; 0)	0 (0; 0)	0 (0; 0)	100 (2.8+; 2.8+)	94 (1.9+; 2.3+)	13 (0.1+; 0.3+)

*Intensity: negative (0), weak (1+), moderate (2+), or strong (3+). Extent: negative (0), focal (1+; <25%), intermediate (2+; 25% to 75%), diffuse (3+; > 75%).
†Stained biliary ductules only.
NP indicates not performed.

to anticipate a behavior different from other teratomatous elements. Last, HCC is chemorefractory, but survival may be improved in the face of metastatic disease by specific tyrosine kinase inhibitors. It is clear, therefore, that the differentiation of these neoplasms from one another is important.

Our study indicates features that allow the distinction of HYST from HCC. In general, HYSTs occurred in younger patients (median, 39 y; range, 25 to 63 y) compared to those with HCCs (median, 63.5 y; range, 49 to 79 y), although there was overlap in the age ranges. Furthermore, HYST represented a late recurrence in at least two-thirds of cases, occurring 2 to 24 years after the initial diagnosis, at a median of 16 years, in this group. Our findings are in line with those of Michael et al,[4] who found that YST was the most common tumor type in late recurrences other than a teratoma, and hepatoid morphology occurred in 19% of those. In that series, HYST was found 4 to 13 years after initial diagnosis (median, 8.5 y) at a median age of 31.5 years (range, 26 to 44 y). Because of the potential for germ cell tumor recurrences to occur as much as 40 years after initial treatment,[9–11] it is apparent that age alone cannot be used to make the distinction of HYST and HCC, especially given that age at diagnosis of HCC has trended down in the United States and most commonly develops in patients 30 to 50 years old in African and Asian countries.[12,13] On microscopic examination, there is overlap between HYST and HCC; both commonly show nested, trabecular and pseudoglandular architecture. Overt bile production strongly favors HCC over HYST; we have only seen bile in a single example of HYST in our experience,[14] whereas it occurred in 44% of our HCCs. Mallory-Denk bodies were also restricted to HCCs and, on the other hand, foci of intercellular basement membrane deposits occurred only in HYSTs. In difficult cases, immunohistochemistry is diagnostic. HYSTs were uniformly positive for SALL4, which is in keeping with what others have found in general studies of YSTs,[15] but our HCCs were negative, similar to the findings in other studies that reported negative or only rare reactivity of HCC for SALL4,[16,17] although other publications have reported a greater proportion of HCCs with SALL4 reactivity.[18] We also found that immunoreactivity for CK19, CDX2, and villin, although less sensitive than SALL4, were also specific in this differential diagnosis, with frequent positivity in HYST and consistent negativity in HCC.

Given the relatively bland cytologic features and the abortive organoid morphology, with associated fibrous bands containing biliary ductule–like structures and rare portal tract-like foci, we concluded that 2 of our cases represented "HTs." Teratoma is a common finding in metastatic deposits resected after chemotherapy for testicular germ cell tumors, but we are not aware of any prior example of metastatic testicular teratoma with hepatic differentiation. Given that pure teratoma in retroperitoneal lymph node resections has an excellent prognosis, it is clearly important to distinguish these lesions from both metastatic HYST and HCC. Morphology alone is usually sufficient since both HYST and HCC show

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

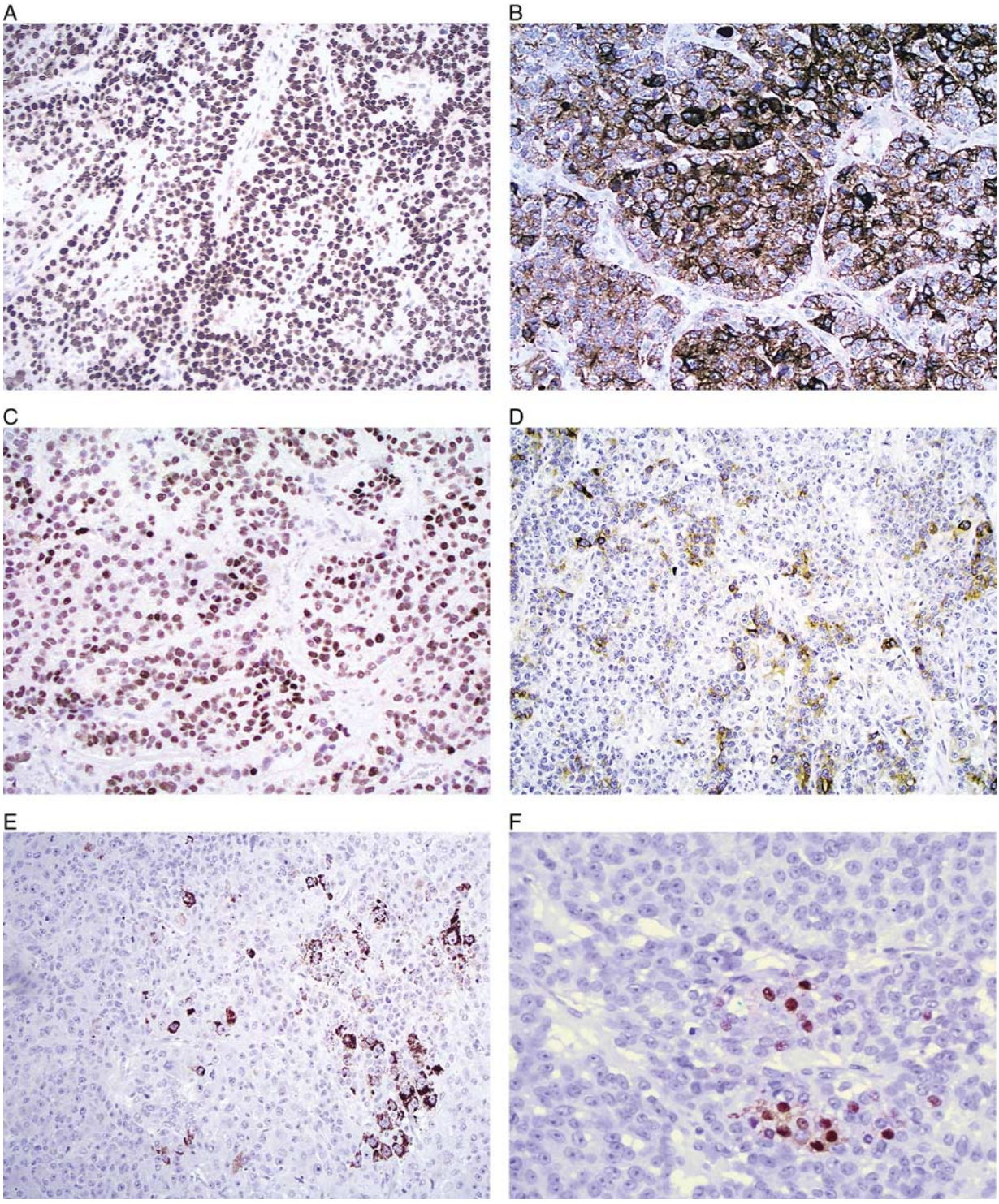

FIGURE 2. HYSTs showing strong and diffuse nuclear immunoreactivity for SALL4 (A), and cytoplasmic positivity for glypican-3 (B), moderate to strong nuclear immunoreactivity for CDX2 (C), and patchy cytoplasmic reactivity for CK19 (D). Only a few tumor cells react with HepPar-1 antibody (E). Arginase immunostain shows nuclear and cytoplasmic immunoreactivity in scattered cells (F).

significantly higher grade atypia and do not show the organoid features of HT. Although cases of combined HCC and cholangiocarcinoma are well known, the ductular component in these is not restricted to fibrous bands but forms invasive nodular growths. There are also immunohistochemical differences between HT and both HYST and HCC. HT, unlike HYST, is SALL4 and CDX2 negative and more frequently arginase positive. The highlighting of ductule-like elements by

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

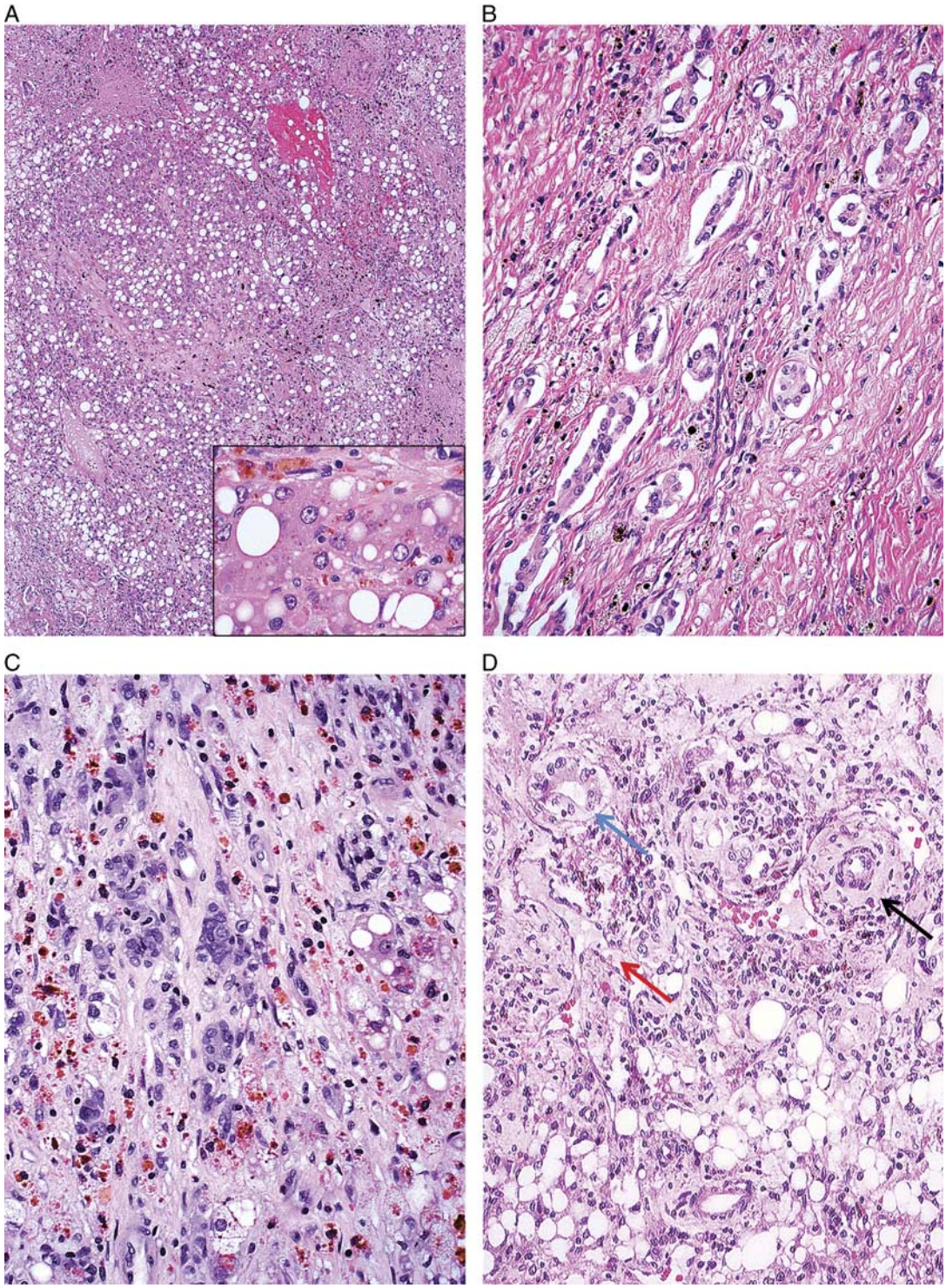

FIGURE 3. HTs showing sheets of hepatocyte-like cells with abundant eosinophilic cytoplasm and macrovesicular fat subdivided into lobules by fibrous bands containing hemosiderin (A). There is little cytologic atypia (A, inset). B, Well-formed biliary ductule–like structures in a fibrous band. C, Poorly formed ductules and siderophages in a fibrous band adjacent to steatotic hepatocytes. D, A portal-like area containing a bile duct (blue arrow), arteriole (black arrow), and venule (red arrow), with adjacent hepatocyte-like cells with macrovesicular fat.

CK19 in HT also helps distinguish it from HCC. The immunohistochemical differences between HT and both HYST and HCC also bolster the evidence that HT is a distinct lesion.

Well-differentiated liver tissue in testicular teratomas is exceedingly rare. Nakashima et al[19] examined 516 germ cell tumors of diverse origin for the presence of hepatic

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

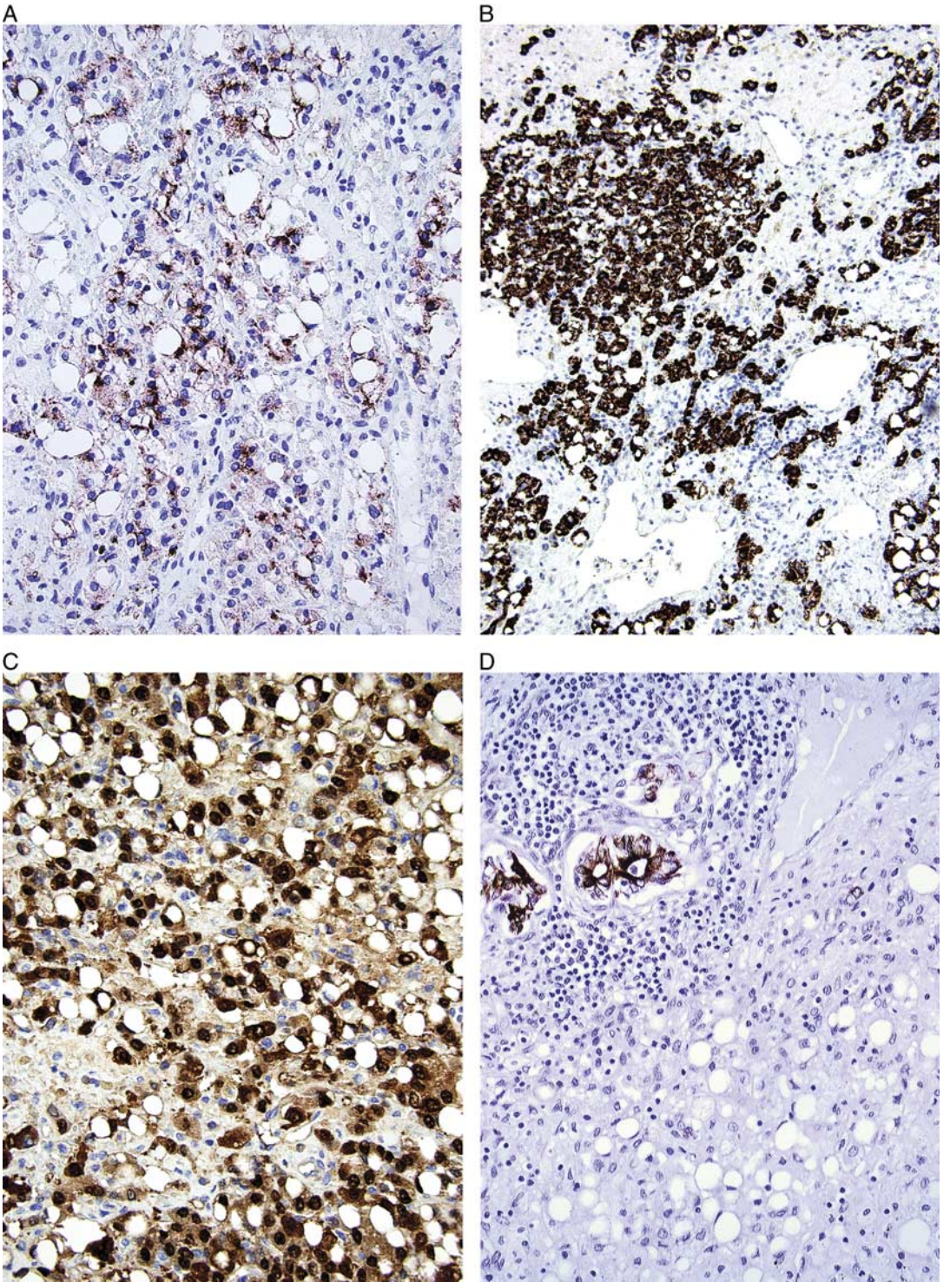

FIGURE 4. HTs showing strong positive immunoreactivity for glypican-3 (A), HepPar-1 (B), arginase (C), and focal positivity in biliary ductules for cytokeratin 19 (D).

tissue and found 7 testicular cases in young men; 5 of these cases also contained YST, and none showed a mature hepatic phenotype. It is unclear if some or all of their cases represent hepatoid differentiation of YST rather than a teratoma, but in none were portal triads found. Jain et al[20] reported a mixed testicular germ cell tumor with foci of HCC showing infiltrative growth and overt cytologic atypia. We have not seen the development of a bona fide

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 3. Clinicopathologic Characteristics of the HCC Control Group (N = 16)

Case No.	Age (y)	Sex	Specimen	Location (Lobe)	Size (cm)	Multifocality	Degree of Differentiation	Background Liver (Nontumoral)	Prominent Light Microscopic Features
1	55	Male	Partial hepatectomy	Right	3.6	No	Moderate	Cirrhosis	Trabecular and pseudoacinar architecture, clear cell features, steatosis
2	60	Male	Partial hepatectomy	Right	3.9	No	Moderate	Steatohepatitis, cirrhosis (radiologic)	Trabecular architecture
3	49	Male	Total hepatectomy	Right/left	3.2	Yes	Well	Cirrhosis	Trabecular and pseudoacinar architecture
4	69	Male	Partial hepatectomy	Left	20	No	Moderate	Cirrhosis	Trabecular and pseudoacinar architecture, Mallory-Denk bodies
5	67	Male	Total hepatectomy	Right	3	No	Moderate	Cirrhosis	Trabecular architecture, clear cell features
6	65	Male	Total hepatectomy	Left	1.2	Yes	Well	Cirrhosis, HCV	Pseudoacinar architecture, Mallory-Denk bodies
7	79	Male	Partial hepatectomy	Right	10.4	Yes	Poor	Ductular reaction	Trabecular architecture, clear cell features, Mallory-Denk bodies
8	63	Male	Partial hepatectomy	Left	7.7	Yes	Well	Bridging fibrosis, HCV	Pseudoacinar architecture
9	71	Male	Partial hepatectomy	Right	10	No	Moderate	Mild steatosis	Trabecular and pseudoacinar architecture
10	65	Male	Partial hepatectomy	Right	5.5	No	Well	Mild portal inflammation	Trabecular architecture, Mallory-Denk bodies
11	55	Female	Partial hepatectomy	Left	24.5	No	Well	Chronic portal inflammation, ductal plate malformation	Pseudoacinar architecture, steatosis
12	60	Male	Total hepatectomy	Right	5	Yes	Moderate	Cirrhosis, HCV	Trabecular and pseudoacinar architecture, Mallory-Denk bodies
13	51	Male	Total hepatectomy	Right	3.2	No	Well	Cirrhosis, cholestasis	Trabecular and pseudoacinar architecture, Mallory-Denk bodies
14	55	Female	Biopsy	Right	20	Yes	Moderate	Cirrhosis (radiologic)	Trabecular and pseudoacinar architecture, hyalinized bands
15	73	Male	Biopsy	Left	9.6	No	Moderate	Noncirrhotic (radiologic)	Trabecular and pseudoacinar architecture, steatosis, Mallory-Denk bodies
16	64	Male	Total	Right	3	Yes	Well	Cirrhosis, NASH	Pseudoacinar architecture, steatosis, Mallory-Denk bodies

HCV indicates hepatitis C virus; NASH, nonalcoholic steatohepatitis.

HCC in a testicular germ cell tumor. Presumably, such a case would show the usual features of liver-based HCC and the immunohistochemical properties we found in this study. Clearly, the distinction of such a case from usual HCC must rely on the association with germ cell tumor elements and/or distribution of any secondary deposits. Regardless, the findings in both studies contrast with those of the 2 HTs we herein report. In our review of the literature, we could find no comparable case of postpubertal-type teratoma of testicular germ cell tumor origin that showed an organoid hepatic phenotype.

In summary, HT is a rare lesion that may be found in postchemotherapy specimens of patients with testicular germ cell tumors and that has unique morphologic and immunohistochemical findings contrasting with those of its 2 potential mimickers—HYST and HCC. It is important to make its distinction from these more prognostically ominous neoplasms, which often require quite different management.

REFERENCES

1. Ulbright TM, Roth LM, Brodhecker CA. Yolk sac differentiation in germ cell tumors. A morphologic study of 50 cases with emphasis on hepatic, enteric, and parietal yolk sac features. *Am J Surg Pathol*. 1986;10:151–164.
2. Ulbright TM, Young RH. Testicular and paratesticular tumors and tumor-like lesions in the first 2 decades. *Semin Diagn Pathol*. 2014;31:323–381.
3. Ulbright TM. Germ cell tumors of the gonads: a selective review emphasizing problems in differential diagnosis, newly appreciated, and controversial issues. *Mod Pathol*. 2005;18(suppl 2):S61–S79.
4. Michael H, Lucia J, Foster RS, et al. The pathology of late recurrence of testicular germ cell tumors. *Am J Surg Pathol*. 2000;24:257–273.
5. Moch H, Cubilla AL, Humphrey PA, et al. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part A: renal, penile, and testicular tumours. *Eur Urol*. 2016;70:93–105.
6. Logothetis CJ, Samuels ML, Trindade A, et al. The prognostic significance of endodermal sinus tumor histology among patients treated for stage III nonseminomatous germ cell tumors of the testes. *Cancer*. 1984;53:122–128.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

7. Fox EP, Weathers TD, Williams SD, et al. Outcome analysis for patients with persistent nonteratomatous germ cell tumor in postchemotherapy retroperitoneal lymph node dissections. *J Clin Oncol*. 1993;11:1294–1299.
8. Carver BS, Shayegan B, Serio A, et al. Long-term clinical outcome after postchemotherapy retroperitoneal lymph node dissection in men with residual teratoma. *J Clin Oncol*. 2007;25:1033–1037.
9. Pavic M, Meeus P, Treilleux I, et al. Malignant teratoma 32 years after treatment of germ cell tumor confined to testis. *Urology*. 2006;67:846.e11–846.e13.
10. Mukhtar S, Beatty J, Agrawal S, et al. Germ cell tumour: late recurrence after 43 years. *Ann R Coll Surg Engl*. 2011;93:e24–e26.
11. Arafat W, Albany C, Ulbright TM, et al. Very late relapse of germ cell tumor as a teratoma: a case report and review of the literature. *J Surg Case Rep*. 2014;2014:rju051.
12. Ghouri YA, Mian I, Rowe JH. Review of hepatocellular carcinoma: epidemiology, etiology, and carcinogenesis. *J Carcinog*. 2017;16:1.
13. Njei B, Rotman Y, Ditah I, et al. Emerging trends in hepatocellular carcinoma incidence and mortality. *Hepatology*. 2015;61:191–199.
14. Ulbright TM, Young RH. *Tumors of the Testis and Adjacent Structures*. Silver Spring, MD: ARP Press; 2013.
15. Cao D, Li J, Guo CC, et al. SALL4 is a novel diagnostic marker for testicular germ cell tumors. *Am J Surg Pathol*. 2009;33:1065–1077.
16. Park H, Lee H, Seo AN, et al. SALL4 expression in hepatocellular carcinomas is associated with EpCAM-positivity and a poor prognosis. *J Pathol Transl Med*. 2015;49:373–381.
17. Liu TC, Vachharajani N, Chapman WC, et al. SALL4 immunoreactivity predicts prognosis in Western hepatocellular carcinoma patients but is a rare event: a study of 236 cases. *Am J Surg Pathol*. 2014;38:966–972.
18. Rittiluechai K, Wilcox R, Lisle J, et al. Prognosis of hepatoid yolk sac tumor in women: what's up, Doc? *Eur J Obstet Gynecol Reprod Biol*. 2014;175:25–29.
19. Nakashima N, Fukatsu T, Nagasaka T, et al. The frequency and histology of hepatic tissue in germ cell tumors. *Am J Surg Pathol*. 1987;11:682–692.
20. Jain D, Mittal S, Gupta M. Hepatocellular carcinoma arising in a testicular teratoma: a distinct and unrecognized secondary somatic malignancy. *Ann Diagn Pathol*. 2013;17:367–371.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.