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Diagnostic importance of hepatocyte nuclear factor 1 beta (HNF1ß) in testicular tumors and its sensitivity for the detection of yolk sac tumors: an immunohistochemical analysis

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ABSTRACT

Objectives: Testicular tumors are common solid malignancies in young fertile men, and most are germ cell tumors. In general, they originate from a single germ cell and transform into different tumor types or present with the coexistence of different morphological patterns. Due to the heterogeneity of these tumors, immunohistochemical markers are frequently used in their differential diagnosis. In recent years, some studies have indicated hepatocyte nuclear factor 1 beta (HNF1β) can be used in the differential diagnosis of testicular tumors, especially yolk sac tumors (YSTs). In this study, we aimed to investigate the general expression status of HNF1β in all testicular tumors and determine its importance in YST detection.

Methods: A total of 144 testicular tumors treated with orchiectomy between 2011 and 2020 were included in our study. The pathological diagnosis reports of these cases were retrospectively reviewed and their general prognostic features were determined. HNF1β immunohistochemical staining was applied to the characteristic paraffin blocks representing the lesions. Staining was evaluated in terms of severity and prevalence.

Results: Most cases (38.2%) were seminomas, followed by mixed germ cell tumors (34.0%, 49/144), embryonic carcinomas (7.6%), pure YSTs (4.9%), and others (Leydig cell tumors, mesenchymal tumors, lymphomas, etc.). No HNF1β immunostaining was observed in any of the seminomatous lesions. A high level of staining was present in almost all the pure YSTs and tumor areas with the YST component. HNF1β had a specificity of 95.1% and sensitivity of 87.1% in the detection of YSTs.

Conclusions: HNF1β has high specificity and sensitivity in detecting YSTs among testicular tumors, and therefore we consider that it can be routinely used to detect the presence of YSTs, especially in patients with mixed germ cell tumors.

Keywords: Testicular germ cell tumor, seminoma, yolk sac tumor, hepatocyte nuclear factor 1 beta (HNF1β)

Testicular cancer is a solid malignancy with an increased global incidence in recent years and is commonly seen in young men [1]. Approximately 95% of these cancer cases are germ cell tumors, constituting 1% of all cancers [2, 3]. According to the 2016 classification of the World Health Organization (WHO), testicular germ cell tumors (TGCTs) are divided into two main groups as those associated and non-associated with intratubular germ cell neoplasia (ITGCN) [4]. TGCTs that are not associated with ITGCN include prepubertal teratomas, prepubertal yolk sac tumors (YSTs), and spermatocytic seminoma,

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while ITGCN-associated TGCTs cause seminomatous and non-seminomatous tumors (Embryonic carcinoma, YST, teratoma, and choriocarcinoma) [5]. In brief, these tumors can originate from a single stem cell and develop into other tumors, leading to the coexistence of different tumor types. There are difficulties in the histopathological differential diagnosis due to the combination of very different histological and morphological patterns and tumor heterogeneity. Therefore, immunohistochemical biomarkers, such as Pan CK, PLAP, CD30, AFP, and OCT3 are widely used to assist differential diagnosis. However, more biomarkers are needed for definitive typing.

The hepatocyte nuclear factor 1 beta (HNF1β) gene was first identified as the factor that regulates the active transcription of liver-specific genes [6]. This gene is localized on the 17q12 chromosome and is also called TCF2 [7]. Four important subtypes of hepatocyte nuclear factor have been defined, among which the HNF1β family is reported to be more closely related to cellular development and tumorigenesis [8]. It has been reported that mutations in this gene cause diabetes, kidney cysts, genital malformations, and benign lesions such as pancreatic atrophy, as well as some malignancies of organs such as the liver, kidney, and ovary [9]. Many genetic and epigenetic changes of the HNF1β gene are considered to play a role in the development and progression of a tumor. It has been reported that the CpG island on the HNF1β' gene is overexpressed in ovarian clear cell carcinomas due to hypomethylation, and this has a diagnostic feature. It has also been suggested that changes in the gene family affect the prognosis of some tumors and the survival of the patient [10].

In recent years, some studies have indicated that HNF1β may be useful in differentiating YSTs from other germ cell tumors [11, 12]. In our study, we aimed to determine the role of the HNF1β immunomarker in the differentiation of different histological types through its expression profile in testicular tumors, and especially in pure YSTs and mixed germ cell tumors (MGCTs). In addition, the relationship of this marker with some prognostic parameters was investigated.

METHODS

Various testicular tumors of 144 cases who underwent partial/total orchiectomy at Atatürk University Medical Faculty Hospital between 2011 and 2021 and were diagnosed at the Department of Pathology were included in the study. The pathology reports of the cases were retrospectively reviewed from the hospital information system. Tumor type, patient age, tumor side, necrosis, bleeding, lymphovascular, perineural, rete testis, epididymis, tunica albuginea, tunica vaginalis, perihilar adipose tissue, spermatic cord invasion, presence of tumor at the surgical margin, lymph node involvement, pathological stage, metastasis, and survival prognostic features were determined. HNF1β immunohistochemical staining was applied to the most suitable samples obtained from paraffin blocks containing tumors. Staining was evaluated in terms of prevalence and intensity. Findings were compared according to tumor types and some prognostic parameters.

This research was ethically approved by the ethics committee of Atatürk University School of Medicine with the decision number 17.06.2020/16.

Immunohistochemical Staining and Interpretation

Sections of 4-micron thickness were taken from the most suitable samples from paraffin tissue blocks fixed with formalin. Immunohistochemical staining was performed using the Ventana BenchMark ULTRA automated stainer (Roche, Basel, Switzerland) according to the manufacturer's protocol. The tissues were stained with a mouse antibody against the HNF1β protein (mouse monoclonal, anti-HNF1β antibody (CLO0374) ab236759, dilution 1:100, ABCAM) with the Ventana BenchMark ULTRA automated stainer. A citrate buffer (pH 6.0) was used for heat-induced epitope recruitment. The primary antibody was visualized with the OptiView DAB IHC Detection Kit (Ventana, Roche). Only nuclear staining was considered positive in HNF1β immunohistochemistry. The presence of staining greater than 1% in the tumoral area was considered positive. Staining was scored from 0 to 3 as follows: negative or 0, no staining; 1+ = weak, 2+ = intermediate and 3+ = strong positive. The expression of HNF1β was evaluated by two independent pathologists [13].

Statistical Analysis

The Pearson/Spearman correlation test was used to determine the correlation between HNF1B staining

and prognostic parameters. A p value of < 0.05 was accepted to indicate significant differences. Data analysis was performed using IBM SPSS statistics v. 20

RESULTS

Orchiectomy materials belonging to 144 individuals in total were included in the study. The mean age of the patients was 33.46 years. Seventy-three tumors were localized in the left testis and 71 in the right testis. Seminomas constituted the majority of cases at a rate of 38.2% (55/144), followed by MGCTs (34.0%, 49/144), embryonic carcinomas (7.6%, 11/144), YSTs (4.9%, 7/144), Leydig cell tumors (3.5%, 5/144), different types of lymphoma (5.5%, 8/144), pure teratomas (4.1%, 6/144), and mesenchymal tumors (2.0%, 3/144; one osteosarcoma, one liposarcoma, and one leiomyoma). Of the cases diagnosed with MGCTs,

Table 1. Distribution of cases according to tumor types and prognostic features

		Seminoma (n = 55)	MGCT (n = 49)	EC (n = 11)	YST (n = 7)	TeRT (n =6)	Leydig (n = 5)	Total (n = 144)
Side, n (%)	Right	27 (49.)	25 (51.)	5 (45.4)	3 (42.8)	2 (33.3)	2 (40)	71 (49.3)
	Left	28 (51.0)	24 (48.)	6 (54.6)	4 (57.2)	4 (66.6)	3 (60)	73 (51.7)
Metastasis, n (%)	Present	10 (18.1)	16 (32.)	2 (18.1)	3 (42.8)	0	0	41 (28.5)
	Absent	45 (81.2)	34 (69.)	9 (91.8)	4 (57.2)	6 (100)	5(%100	103 (71.9
Size, n (%)	≤ 3 cm	16 (29.1)	13 (26.)	6 (54.6)	4 (57.2)	1 (16.6)	1(%20)	43 (29.8)
	> 3 cm	39 (70.9)	36 (73)	5 (45.4)	3 (42.8)	5 (83.4)	4(%40)	101 (70.2
Necrosis, n (%)	Present	31 (56.3)	42 (85.79	2 (18.1)	2 (28.5)	0	1 (20)	85 (59.0)
	Absent	24 (43.7)	7 (14.2)	9 (91.8)	5 (71.5)	6 (100)	4 (80)	59 (410.)
Bleeding, n (%)	Present	8 (14.5)	36 (73.4)	9 (91.8)	2 (28.5)	0	1 (20)	58 (40.2)
	Absent	47 (85.5)	13 (26.6)	2 (18.1)	5 (71.5)	6 (100)	4 (80)	86 (59.39
LVI, n (%)	Present	30 (54.5)	35 (71.59	8 (72.8)	3 (42.8)	0	1 (20)	83 (57.6)
	Absent	25 (45.5)	14 (28.5)	3 (27.2)	4 (57.2)	6 (100)	4 (80)	61 (42.3)
Rete, n (%)	Present	23 (41.8)	17 (34.6)	8 (72.8)	2 (28.5)	0	0	60 (41.79
	Absent	32 (58.2)	32 (65.3)	3 (27.2)	5 (71.5)	6 (100)	5 (100	84 (58.39
Vaginalis, n (%)	Present	8 (14.5)	4 (58.1)	1 (9)	0	0	0	16 (11.1)
	Absent	47 (85.5)	45 (91.9)	10 (91	7 (100)	6 (100)	5 (100)	128 (88.9
Epididymis, n (%)	Present	7 (12.7)	6 (12.2)	0	0	0	0	16 (11.1)
	Absent	48 (87.3)	43 (87.8)	11 (100	7 (100)	6 (100)	5 (100)	128 (88.9
Perihilar, n (%)	Present	7 (12.7)	6 (12.2)	0	0	0	0	14 (9.8)
	Absent	48 (87.3)	43 (87.8)	11 (100	7 (100)	6 (100)	5 (100)	130 (90.2
Spermatic cord, n (%)	Present	2 (3.6)	3 (6.1)	1 (9)	0	0	1 (20)	9 (6.2)
	Absent	53 (96.4)	46 (93.9)	10 (91)	7 (100)	6 (100)	4 (80)	135 (93.8
Surgical margin, n (%)	Present	1 (1.8)	0	0	0	0	0	1 (0.6)
	Absent	54 (98.2)	49 (100)	11 (100	7 (100)	6 (100)	5 (100)	141 (98)
pT, n (%)	1	23 (41.8)	15 (30.6)	4 (36.6)	3 (42.8)	6 (100)	4 (80)	63 (43.7)
	2	28 (50.9)	31 (63.2)	7 (63.4)	4 (57.2)	0	1 (20)	71 (49.3)
	3	4 (7.2)	3 (6.1)	0	0	0	0	10 (7)
In situ component, n (%)	Present	42 (76.4)	42 (85.7)	10 (91)	3 (42.8)	0	0	97 (67.3)
	Absent	135 (23.6)	7 (14.3)	1 (9)	4 (52.2)	6 (100)	5 (100)	47 (32.6)
Mortality status, n (%)	Survive	2 (3.6)	2 (4.0)	0	0	0	1 (20)	12 (8.3)
	Died	53 (96.4)	47 (96)	11 (100	7 (100)	6 (100)	4 (80)	132 (91.7

MGCT = Mixt Germ Cell Tumor, EC = Embrional Carcinoma, YST = Yolk Sac Tumor, TeRT = Teratoma, Leydig = leydig cel tumor, LVI = Lymphovascular invasion, pT =Patholojic stage

39 had embryonal carcinomas, 34 had seminomas, 31 had YSTs, and 13 had teratoma components. The choriocarcinoma component was observed in four cases.

Tumor size was below 3 cm in 43 (29.9%) cases and over 3 cm in 101 (70.1%). While metastasis was observed in 41 (28.6%) cases, the tumor was limited to the testis in 103 (71.5%) patients. Most of the metastases were those of MGCTs. Lymphovascular invasion was observed in 88% (127/144) of the cases. The highest pathological stage was seen in the pT2 group including 71 (49.3%) cases. The presence of carcinoma in situ was detected in 102 (70.8%) cases. A total of 132 of the cases are still alive, while the remaining 12 died. Of the patients that died, six had lymphomas, two had MGCTs, two had seminomas, and two had sarcomas. Other findings are summarized in Table 1.

Immunohistochemical distribution with HNF1β

Staining was graded as 3+ in 32 of these cases, 2+ in five, and 1+ in two (Figs. 1 and 2). Of the cases diagnosed with MGCTs, two were interpreted as YSTs but did not present with HNF1β staining. On the other hand, 1+ HNF1β staining was observed in the embryonal carcinoma areas in five cases with MGCTs (Figs. 1 to 3). HNF1β staining was not observed in any of the seminomas and seminomatous areas of the MGCTs (Figs. 1D and 3B). Lymphomas, mesenchymal tumors, and Leydig cell tumors included in the study, while it was present in almost all the pure YSTs and YST components of the MGCTs (39/41). More than 70% of the cases diagnosed with pure YSTs and the YST areas in cases diagnosed with MGCTs had HNF1β staining. HNF1β staining was graded as 3+ in all the teratomatous areas. No staining was observed in the lymphomas (Fig. 3D) or the choriocarcinomatous areas (Fig. 3E). The main immunohistochemical findings and their comparison according to other YST markers are summarized in Table 2. In our study, the sensitivity of HNF1B in terms of detecting the YST component was 87.1%, and the specificity was 95.1%.

No significant correlation was found between HNF1B staining and histopathological and clinical prognostic parameters such as necrosis, lymphovascular invasion, perineural invasion, rete testis invasion, perihilar adipose tissue invasion, spermatic cord invasion, lymph node involvement, pathological stage, metastasis and survival etc. ($p > 0.005$). No significant correlation was found between HNF1B staining and

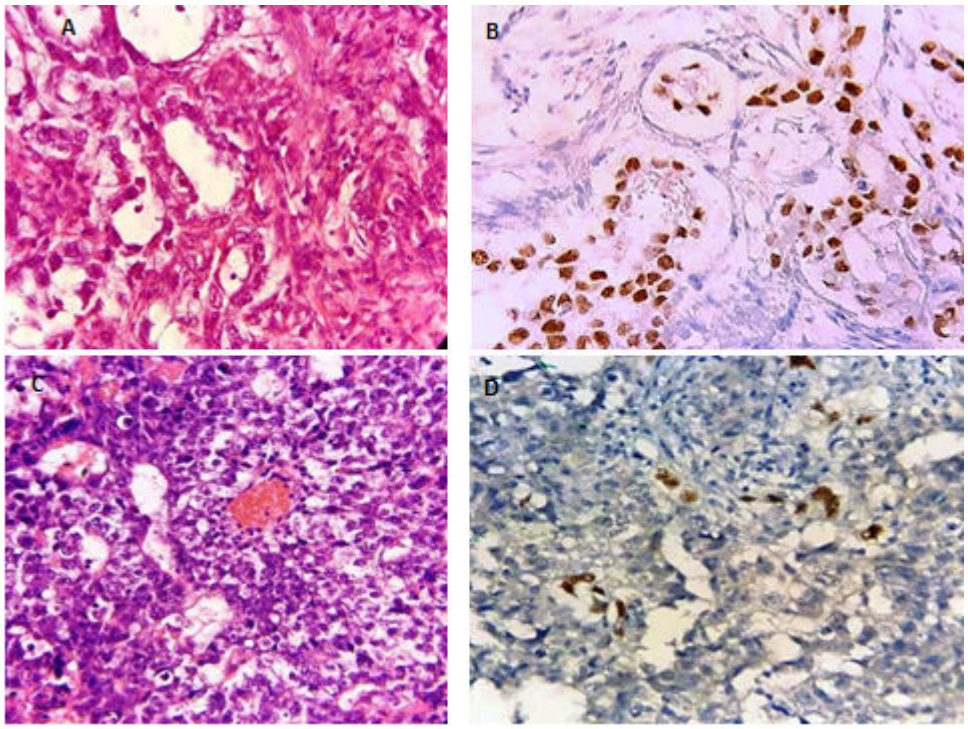

Fig. 1. HNF1B expression in MGCT component YST and Pure YST. (A) Pure YST with the microcystic pattern (HE ×20), (B) Strong nuclear positivity for HNF1β in YST (HNF1β ×20), (C) Mixed germ cell tumor with YST component (HE ×20), and (D) Nuclear positivity for HNF1β in the YST component of MGCT (HNF1β ×20).

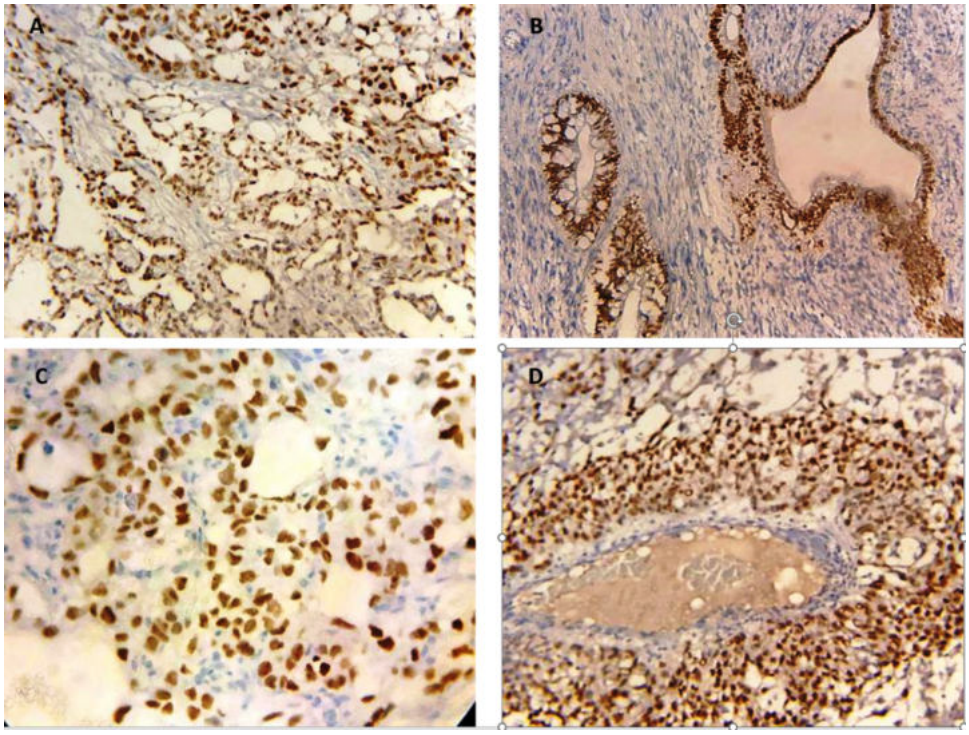

Fig. 2. HNF1β expression in different patterns of YST. (A) Diffuse nuclear positivity for HNF1β in YST with the microcystic pattern (HNF1B ×20), (B) Glandular pattern YST (HNF1β ×20), (C) Solid pattern YST (HNF1β ×20), and (D) Mixed pattern YST (HNF1β ×20).

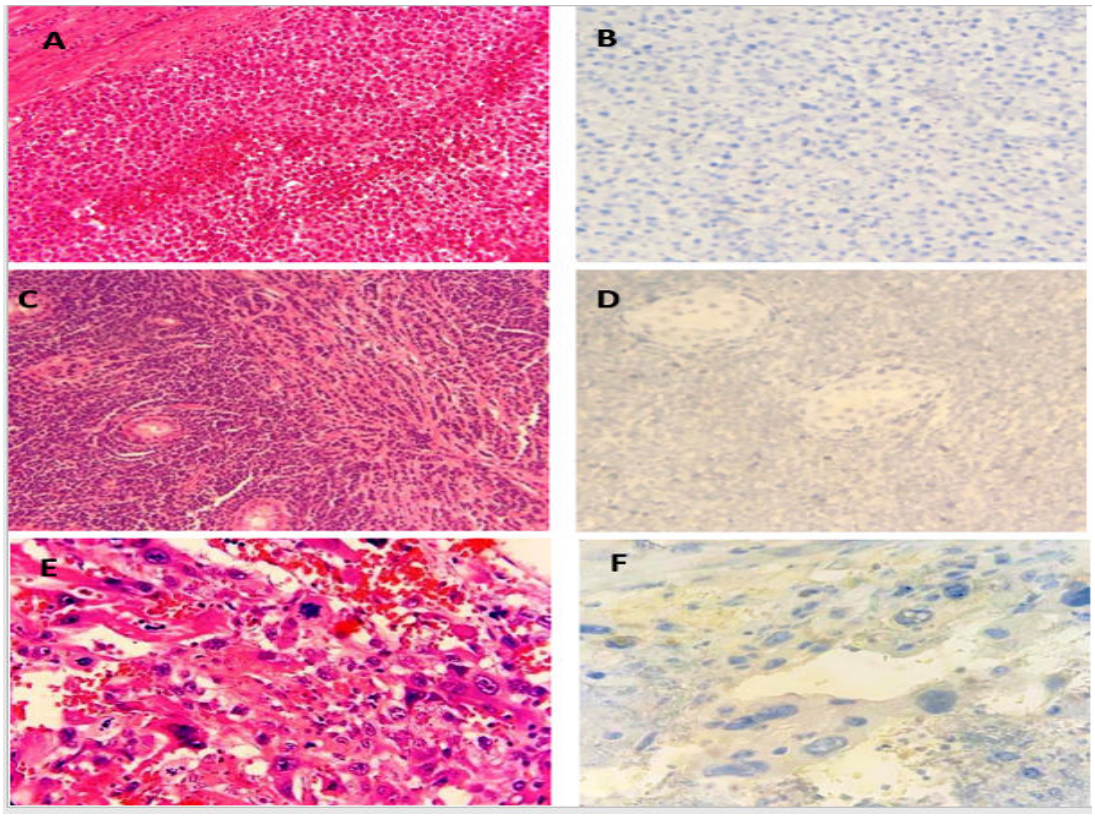

Fig. 3. HNF1β expression profile in different tumor types and areas. (A) Seminoma (HE ×20), B-Negative HNF1β staining in seminoma (×20), (C) Intratesticular lymphoma (HEx20), (D) Negative HNF1β staining in intratesticular lymphoma (×20), (E) Choriocarcinomatous area in MGCT (HEx40), and (F) Negative HNF1β staining in the choriocarcinomatous area of MGCT (×40)

histopathological and clinical prognostic parameters such as necrosis, lymphovascular invasion, perineural invasion, rete testis invasion, perihilar adipose tissue invasion, spermatic cord invasion, lymph node involvement, pathological stage, metastasis and survival etc. ($p > 0.005$). A significant difference was observed between YST and other histological types with the Chi-square test, which supports the specificity and sensitivity tests, with HNF1B ($p < 0.001$). When histological types were examined separately, a significant difference was observed between embryonal carcinoma ($p < 0.001$) and seminoma ($p < 0.001$).

DISCUSSION

Although testicular germ cell tumors constitute less than 1% of all tumors in men, they are the most common tumors of the testis. Their prevalence in young fertile men makes them particularly important. Depending on their development from intratubular germ cell neoplasia, they may contain seminomatous and non-seminomatous, or embryonal and extra-embryonal differentiation areas, or all these areas together. Due to their heterogeneity, it is difficult to make an accurate diagnosis of testicular germ cell tumors. The accuracy of diagnosis is very important in terms of case management and treatment [14].

MGCTs and especially YSTs have many morphological patterns, making the diagnosis very difficult. Numerous immunohistochemical markers are used to distinguish tumor types and patterns. Alpha-fetoprotein (AFP) and glypican-3 are the most well-known examples of these markers. Some studies conducted in recent years state that HNF1β is an important YST marker [11, 12].

HNF1β was identified as a liver-specific transcription factor. It has been suggested to play a role in liver, pancreas, and kidney organogenesis, and mutations in this gene have been associated with diabetes, kidney cysts, genital malformations, and benign lesions such as pancreatic atrophy [9], as well as cancer risk in various tumors, including hepatocellular carcinoma, pancreatic, renal, ovarian, endometrial, and prostatic cancers [15, 16].

Many genetic and epigenetic changes of the HNF1β gene are considered to play a role in the development and progression of a tumor. In humans, one of the epigenetic mechanisms regulating the expression of genes is the methylation of CpG dinucleotide

Table 2. Distribution of HNF1β expression according to tumor types (n = 144)

Tumor type		HNF1β			
		0	1+	2+	3+
Seminoma, n (%)	**n = 55**	55 (100)	0	0	0
MGCT, n (%)	**n = 49**				
YST	34 (69.3)	2 (5.8)	2 (5.8)	4 (11.7)	26 (76.7)
EC	39 (79.5)	34 (87.1)	5 (12.8)	0	0
Seminoma	31 (63.2)	31 (100)	0	0	0
Teratoma	13 (26.5)	2 (15.4)	2 (15.4)	3 (23)	6 (46.2)
Choriocarcino	4 (8.1)	4 (100)	0	0	0
Pure YST, n (%)	**n = 7**	0	0	1 (14.29	6 (85.8)
EC, n (%)	**n = 11**	9 (81.8)	2 (18.2)	0	0
Teratoma, n (%)	**n = 6**	0	0	1 (16.7)	5 (83.3)
Lymphoma, n (%)	**n = 8**	8 (100)	0	0	0
Leydig cell tumor, n (%)	**n = 5**	5 (100)	0	0	0
Mesenchymal tumor, n (%)	**n = 3**	3 (100)	0	0	0
Total	**144**				

HNF1β = hepatocyte nuclear factor 1 beta, MGCT = mixed germ cell tumor, YST = yolk sac tumor, EC = embryonal carcinoma

clusters. It is stated that HNF1β is overexpressed in clear cell carcinomas of the ovary due to the hypomethylation of the CpG island on the HNF1β' gene [1]). It has been suggested that the epigenetic inactivation of HNF1β is involved in tumorigenesis [17]. Some studies have reported that HNF1β plays a role in the expression of genes closely related to stem/progenitor cells [18]. However, the potential pathogenic mechanisms of HNF1β in cancer and regulatory mechanisms in stem cells are not yet fully understood. Therefore, further studies are still needed to elucidate the relationship between tumor and stem cell and HNF1β [19].

In a study by Shim *et al*. [20], the members of the HNF1 family were reported to regulate the activity of the AFP promoter during hepatic development and carcinogenesis process, and therefore a high HNF1β expression in hepatocellular carcinomas was associated with a high serum AFP level and AFP expression.

HNF1β has been identified as an important biomarker in clear cell carcinomas of the uterus and ovary in many gene expression studies. It has been reported that while HNF1β is highly expressed in ovarian clear cell carcinomas (CCC), non-CCCs do not express this protein [21]. Yamamoto *et al*. [22]suggested that the prevalence of HNF1β immunoreactivity in both the ovary and the endometrium would be an excellent marker for differentiating CCCs from other tumors. Kao *et al*. [23] stated that the overexpression of HNF1β was specific to ovarian CCC among ovarian carcinomas. In the pancreas, Kim *et al*. [24] showed that clear cell carcinomas and ductal carcinomas with clear cell features were overexpressed in clear cell components and were associated with worse survival. In another study, Silva *et al*. [25] showed HNF1β to be among five important genes that played an epigenetic role in colorectal cancer. They stated that HNF1β could be used as a useful biomarker in this cancer [25].

Buchner *et al*. [26] reported that HNF1β had a high expression in normal kidney tissue than in tumor tissue, and its loss was associated with renal cell carcinoma. They also suggested that HNF1β might be a tumor suppressor prognostic factor and therapeutic target [26]. In a study by Nogales *et al*. [27], it was determined that HNF1β was highly expressed in ovarian clear cell carcinoma and germ cell tumors with the glandular yolk sac pattern. Fadare *et al*. [28] reported that while HNF1β showed nuclear expression in 92% of ovarian clear cell carcinomas and 100% in YSTs, it was not stained in granulosa cell tumors or dysgerminomas. In a study by Rougemont *et al*. [11] evaluating 45 germ cell tumors, HNF1β staining was present in all the pure YSTs and YST components of the tumoral areas, and it was graded as 3+ in 93.9% of the cases. The authors stated that HNF1β had 100% sensitivity and 80% specificity for the detection of YSTs. In the same study, there was no staining in the seminomas or ECs, but staining was noted in the enteric type glandular areas of the teratomas [11].

Gallo *et al*. [12], comparing the expression of AFP, glypican-3 and HNF1β in 601 testicular germ cell tumors, determined their specificity as 97.7%, 90.3%, and 96.5%, respectively and their sensitivity as 62.5%, 83.3%, and 85.4%, respectively in the detection of YSTs. Accordingly, HNF1β had a higher rate of YST detection than the other two markers. Thus, the authors suggested that HNF1β could be a very important and reliable biomarker for distinguishing tumors. They also noted that there was no HNF1β staining among the seminomatous tumors [12].

Similarly, in our study, HNF1β expression was not observed in any of the seminomatous tumors. HNF1β staining was also not observed among the lymphomas, mesenchymal tumors, and Leydig cell tumors in our series. In contrast, significant nuclear positive staining was present in almost all (39/41) the YST components of the non-seminomatous tumors and MGCTs. There was no staining in the majority of the embryonal carcinoma areas. Weak (1+) staining being observed in only five cases suggests that these might be possible YST areas but were misinterpreted as embryonal carcinomas. The staining pattern in the teratomatous areas was consistent with previous studies, and a high level of staining was observed especially in areas with intestinal differentiation.

In our study, HNF1β immunostaining has very high sensitivity (87.1%) and specificity (97.1%) in terms of detecting areas in pure YST and MGCTs containing YST component, which is consistent with the Rougement and Gallo research.

Limitations

Our study has several limitations. Among these, the HNF1β application was applied only to the pri-

mary tumor in the testis and did not include the expression status in metastatic or recurrent tumors. Therefore, further research including our limitations is needed.

CONCLUSION

It is clear that HNF1β plays an important role in the tumorigenesis of various organs. It is an important biomarker used in the differential diagnosis of tumors of some organs, such as clear cell carcinoma of the ovary. A high HNF1β expression is known to be associated with poor prognosis and poor survival in patients with tumors of the liver and pancreas. On the other hand, it is stated that HNF1β is expressed at a lower rate in renal cell carcinomas than in normal kidney tissue. In the literature, the number of studies on HNF1β expression in testicular tumors is very limited. In our study, we tried to reveal the expression profile of HNF1β in all testicular tumors. Therefore, our study is very special in terms of detecting the YST component, especially in germ cell tumors, and the data obtained had high sensitivity and specificity. In light of our findings, we consider that HNF1β can be used as a sensitive and reliable marker in the detection of these tumors. Although HNF1β has high sensitivity and specificity for the diagnosis of YSTs, it is very important to support the diagnosis with tumor morphology and genetic and epigenetic changes.

Author' Contribution

Study Conception: RA; Study Design: RA; Supervision: RA; Funding: RA; Materials: RA; Data Collection and/or Processing: RA; Statistical Analysis and/or Data Interpretation: RA; Literature Review: RA; Manuscript Preparation: RA and Critical Review: RA.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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