PROGRESS IN MEDICAL SCIENCES, 2021
VOL 5, NO. 2, PAGE 1 – 7
DOI: doi.org/10.47363/PMS/2021(5)161

RESEARCH ARTICLE

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Human Chorionic Gonadotropin As A Marker of Testicular Cancer

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ABSTRACT

Testicular cancer is a rare disease, which usually occurs in young and middle-aged men, although it can affect early ages. CT constitutes 2% of all neoplasms in males, being the most common neoplasm between 15 and 35 years of age. However, in recent years diagnostic measures have been described to determine this disease, an example of this are markers such as α-fetoprotein (AFP), the β subunit of human chorionic gonadotropin (b-hCG) and lactate dehydrogenase (LDH) that actively participate in the diagnosis, prognosis, monitoring of the treatment and the evolution of the testicular tumor, being b-HCG the most relevant for its ability to rise in any type of testicular tumor, and can also be observed during the treatment to test its effectiveness in germ cell tumors or to participate in the detection of cancer recurrence after treatment has ended.

ARTICLE HISTORY

Received October 07, 2021
Accepted October 13, 2021
Published October 23, 2021

KEYWORDS

Testicular Cancer, Tumor Markers, Gonadotropin, Hormone

Introduction

Testicular cancer is a frequent neoplasm that has a current cure in most cases, it is not very common; however, they are the most frequent solid malignant tumors in men between the ages of 15 and 34, representing 1% of the various types of cancer [1,2].

Testicular cancer includes a variety of neoplasms, according to the cell of origin and the age of presentation [3]. Most of them originate from germ cells (95%); these are seminomas and not seminomas [4]. Therefore, the germ cell tumor is understood as a neoplasm derived from primordial germ cells that in embryonic age migrate to the undifferentiated gonads. However, within tumor cancers, primary and secondary cancers can be distinguished (Table 1). Within the framework of primary testicular cancers, there are testicular germ cell cancers, which encompass two main histological types such as seminoma, which include classical and spermatocytic, and non-seminomatous germ cell tumors, which include embryonal carcinoma, choriocarcinoma, the yolk sac tumor and teratoma [5]. Additionally, secondary testicular cancers are characterized by having their origin in extratesticular organs that, in a certain way, end up spreading to the testicles and causing testicular cancer.

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Table 1: Classification of Testicular Tumors

PRIMARY TESTICULAR CANCERS			
Germ cell tumors	Seminomas	Classic	
		Spermatocytic	
	No seminomas	Embryonal carcinoma	
		Yolk sac carcinoma	
		Choriocarcinoma	
		Teratoma	Mature teratomas
			Immature teratomas
			Teratoma with somatic-type malignancy
Carcinoma in situ of the testicle			
Stromal tumors	Leydig cell tumors		
	Sertoli cell tumors		
SECONDARY TESTICULAR CANCERS			
Lymphoma			
Leukemia			
Prostate cancer			
Kidney cancer			
Melanoma			

Ct Clinical Criteria

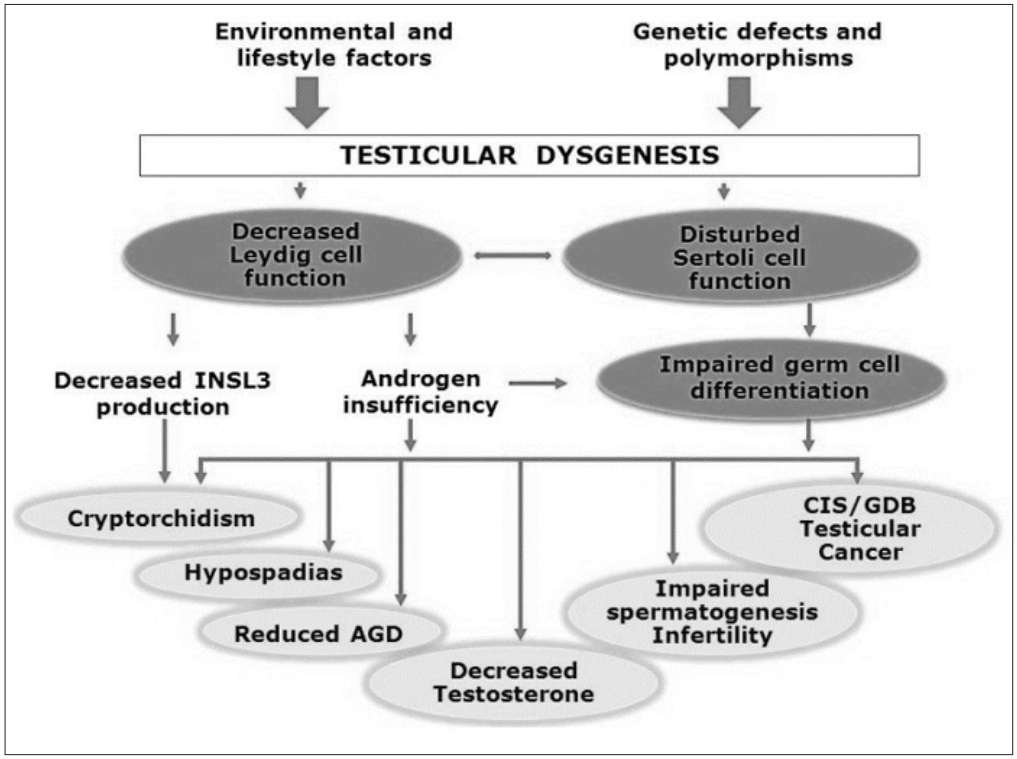
On CT clinically, it is evidenced by the appearance of a painless scrotal nodule or mass that is discovered by the patient accidentally. It is a characteristic that does not generate symptoms; therefore, the patient downplays these findings, goes to the doctor after months of evolution due to the non-disappearance of the initially detected mass. It is also possible that the patient presents with mild testicular pain or localized abdominal pain that radiates to the inguinal area. In very few cases, an inflammation can occur at the testicular level, called orchitis, which can be evidenced as hydrocele or torpid evolution, for this reason, According to the National Comprehensive Cancer Network proposes the stages (Table 2) for clinical staging and follow-up is essential abdominal pelvic tomography and chest radiography [6].

Table 2: TNM Classification for Testicular Cancer

STADIUM	TUMOR	GANGLIA	METÁSTASIS	MARKERS
Stadium 0	pTis	N0	M0	S0, Sx
Stadium 1	pT1-4	N0	M0	Sx
Stadium 1A	pT1	N0	M0	S0
Stadium 1B	pT2-pT4	N0	M0	S0
Stadium IS	Any T/Tx	N0	M0	S1-3
Stadium II	Any T/Tx	N1-N3	M0	Sx
Stadium IIA	Any T/Tx	N1	M0	S0
	Any T/Tx	N1	M0	S1
Stadium IIB	Any T/Tx	N2	M0	S0
	Any T/Tx	N2	M0	S1
Stadium IIC	Any T/Tx	N3	M0	S0
	Any T/Tx	N3	M0	S1
Stadium III	Any T/Tx	Any N	M1a	Sx
Stadium IIIA	Any T/Tx	Any N	M1a	S0
	Any T/Tx	Any N	M1a	S1
Stadium IIIB	Any T/Tx	N1-N3	M0	S2
	Any T/Tx	Any N	M1a	S2
Stadium IIIC	Any T/Tx	N1-N3	M0	S3
	Any T/Tx	Any N	M1a	S3

Ethiopathology of CT

From the etiology of CT, there are some risk factors related to testicular cancer (Figure 2) where the most established are cryptorchidism, the presence of a family history of testicular cancer, and contralateral testicular cancer, among others. In addition to genetic predisposition, studies have been conducted on environmental risk factors and several hypotheses have been explored about exposure to exogenous maternal and intrauterine sources [7].



Useful Markers for Determining TC

In addition to the clinical presentation as a result of malignant characteristics, testicular cancer manifests an alteration in endocrine and reproductive development, which causes an imbalance in hormonal signaling, causing the appearance of secondary endocrine symptoms [8]. Therefore, the recommended serum tumor markers to evaluate include α-fetoprotein (AFP), the β subunit of human chorionic gonadotropin (b-hCG), and lactate dehydrogenase (LDH) [9]. Figure 1 shows the elevation of each of them depending on the type of tumor that is present [10]. Certain tumor germ cells have the ability to synthesize proteins such as α-fetoprotein (αFP) and human chorionic gonadotropin, which are useful, among other things, as tumor markers for diagnosis and monitoring of therapy used against the tumor [11]. Among this type of cells are trophoblastic cells to produce human chorionic gonadotropin (hCG) which is a glycoprotein composed of 244 amino acids (aa), used mainly for the diagnosis of pregnancy or gestational pathologies. However, the clinical utility of the hormone has recently been observed in adult men with germ cell testicular cancer due to increased blood levels (> 5 mIU / ml) similar to those in some stages of pregnancy.

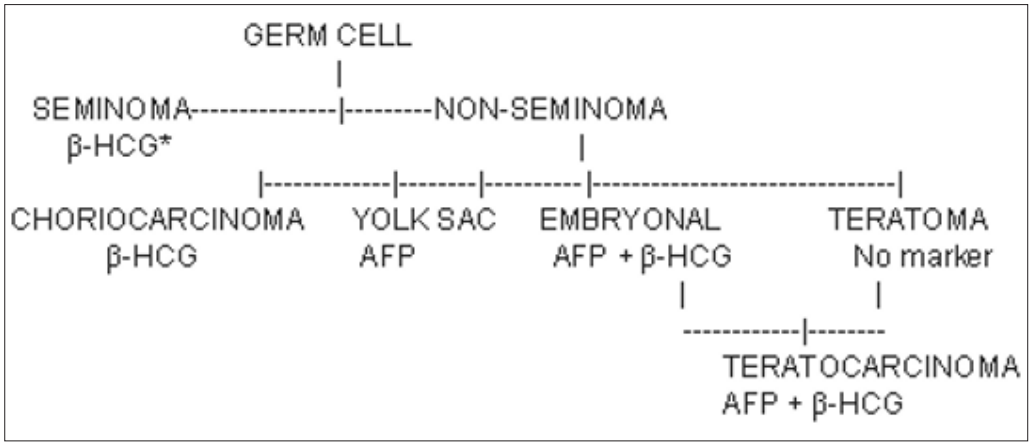


Figure 1: Serum Markers Involved in the Diagnosis of Testicular Cancer

Table 3: Prognostic-Based Staging System in Metastatic Germ Cell Cancer (IGCCCG)

	S0	S1	S2	S3
AFP	Normal markers	<1000 ng/mL	1000-10.000 ng/mL	>10.000 ng/mL
LDH		<1,5 x upper limit of normal	1,5-10 x above normal	> 10 x above normal
hCG		<5000 mUI/mL	5000-50.000 mUI/mL	>50.000 mUI/mL

Importance of HCG as a Determining Marker of TC

Human chorionic gonadotropin (hCG), also known as β-HCG, is a glycoprotein composed of two subunits α and β. Unlike the α subunit, β is immunologically different from other hormones such as LH, FSH or TSH, giving it this specificity and its usefulness as a tumor marker, therefore, it is mainly the one that is measured in blood to establish diagnosis, prognosis, monitoring the treatment and the evolution of the testicular tumor because it can be elevated in any type of testicular tumor, while alpha-fetoprotein only increases in non-seminomatous tumors , therefore, in terms of HCG levels they tend to be elevated in patients with germ cell tumors of gonadal or extragonadal origin and in gestational trophoblastic disease, but also in malignant epithelial neoplasms such as carcinoma of the breast, lung, bladder and gastrointestinal tumors [12,13].

Materials and Methods

A detailed bibliographic search of information published since 2015 is carried out, in the databases pubmed, Elsevier, scielo, national and international libraries. The following descriptors were used: Testicular Cancer biomarkers, human chorionic gonadotropin. The data obtained oscillate between 5 and 18 records after the use of the different keywords. The search for articles was carried out in Spanish and English, it was limited by year of publication and studies published since 2015 were used.

Results

Testicular cancer (TC) represents a low frequency compared to diagnoses of malignant neoplasms (14); around 1 in 250 men will suffer from it at some stage in their life. However, it is the most frequent solid tumor in men during their reproductive age, especially at 33 years, however, around 6% of cases occur in children and adolescents, and around 8% occur in men. over 55 years old. According to the American Society of Clinical Oncology, in 2020, there were an estimated 3,100 new cases between the ages of 30-39 and 3,000 cases between the ages of 20-29. By 2021, the American Cancer Society considers diagnosing approximately 9,470 new cases and 440 cases of male deaths in the United States from this scourge, despite having a high survival rate [15,16]. Likewise, an increase in mortality has been shown in Croatia and Brazil [17]. This indicates that cases have been increasing in recent decades, primarily affecting the Caucasian population. The highest incidence rates are found in Northern and Western European countries, the United States, Australia, and New Zealand, although no increases have been seen in Japan, Switzerland, and China [18,19].

According to statistics from Globocan (a project of the world health organization), the incidence of testicular tumors in Colombia is 2 x 100 thousand inhabitants (and 2.8 performing standardization for age) with a mortality of 0.4% and prevalence at 5 years of 2.9% [20]. Testicular cancer has been well described as one of the few solid organ malignant tumors for which there are several suitable serum markers for evaluation, among these markers is β-hCG. In men, HCG mimics luteinizing hormone and helps to restore and maintain testosterone production in the testes, however, levels of this hormone in healthy men are not usually very high, and increased HCG levels in men is associated with testicular cancer as reported by the Cancer Society of the United States, depending on the type of cancer cell, there may be a high secretion of HCG [21]. For this reason, abnormal levels of HCG plus complementary tests are essential in the diagnosis, staging, prognosis, follow-up of therapy and early identification of this disease. In 90% of cases, an elevation of 1 or 2 markers, but elevated HCG develops in more than 30% of patients [22].

Several studies have been able to verify the importance of the human chorionic gonadotropin hormone as a relevant marker in this disease.

An investigation carried out by Valladares, in 2016, who defined the incidence rates, global and adjusted to risk age, for testicular germ cell tumors. It turned out that the histological type identified in the patients was 62% seminoma and 10% non-seminoma. They determined altered tumor markers for AFP and BHCG in 40% and 31% of patients before surgery [23]. Then, Romero, in 2017, in Ecuador, determined the importance of BHCG as a tumor marker for testicular cancer in men over 40 years of age. 86% of the patients presented BHCG within normal ranges and 14% above normal. 12% of the patients presented a painless mass; therefore, in patients with increased BHCG, there is the presence of testicular cancer [24]. In the same year, Lorenzo et al, (2017). They carried out a descriptive analysis in patients diagnosed with primary testicular cancer and assessed possible predictive factors of tumor recurrence, in order to establish individualized follow-ups. The study included the participation of 91 patients who underwent radical orchiectomy for primary testicular tumor between January 2004 and December 2014. The variables analyzed were: reason for consultation, ultrasound characteristics, tumor markers (AFP, LDH and β-HCG), stage tumor, pathological anatomy, treatment and presence of relapse, in terms of results, it was shown that the mean age was 31.8 ± 10.4 years. The most frequent reason for consultation was painless mass (71.1%), followed by testicular pain (24.4%). On ultrasound, the majority had a single (78.3%) and heterogeneous (85.4%) mass. 71.4% of the cases were in stage I, 24.2% in stage II and 4.4% in stage III. 7 In 55 patients only radical orchiectomy was performed, in 34 chemotherapy was associated and in 2 radiotherapy was applied. During the follow-up time, 14 patients (15.38%) relapsed and one death. Of the 14 relapses, 9 occurred during the first year. The only recurrence predictor detected was an elevated β-HCG level in these patients [25].

Discussion

Testicular neoplasms are malignant tumors for which serum markers have been identified, either individually or in combination, they include human chorionic gonadotropin, alpha-fetoprotein and lactate dehydrogenase. Therefore, it is important to consider that tumor markers are expressed in 15-20% of seminomas and in 60-80% of non-seminomas [26]. In turn, HCG, apart from maintaining the ovarian corpus luteum at the beginning of gestation, is also synthesized to a lesser extent by other tissues. However, significant increases in blood or urine values of the hormone are useful for the diagnosis of a germ cell neoplasm, manifesting itself with precocious puberty in children and with hypogonadism and sexual impotence in adults. In turn, it allows to elucidate the tumor load and the type of cell involved, as in the case of choriocarcinomas, where very high levels of the hormone can be found in the blood and in the case of embryonic carcinomas and mixed carcinomas with the presence of germ cells. the elevation in minor [27]. In addition, 40% and 60% of men with non-seminomatous tumors have elevated β-HCG levels. These serum tumor markers have an important utility for the monitoring of non-seminomatous tumors and metastatic seminomas since their high values are the earliest sign of severity, so their measurement after removal of the cancerous testicle is also appropriate, becoming an important factor for your prognosis. As in the case of 110 patients in whom typical tumor markers were evaluated after an orchiectomy and found α-fetoprotein in 48% of cases, β-human chorionic gonadotropin in 14% and α-fetoprotein and β- Human chorionic gonadotropin in 38%, with a good prognosis in 94% of cases [28]. In most cases, there is an increase in the concentration of HCG. However, negative results may occur in the serum of patients, so the use of the FNA-HGC wash would give us a more precise diagnosis, as in a case report, where an increase in the level of HCG (162 mIU / ml) was detected using this technique [29]. Therefore, it is important to establish new reference limits to increase the clinical utility of HCG detection, since some assays such as Elecsys hCG + β did not reflect the levels found in clinical practice due to the extremely high reference limits [30]. It is also important to consider that HCG quantification can give false positive results due to cross-reactivity with luteinizing hormone, since the beta subunit of HCG is 70% homologous to this hormone [31]. Furthermore, an observational study including 70 patients shows that elevated human chorionic gonadotropin concentrations show significantly lower relapse-free survival ($p = 0.001$) [32]. This makes it one of the most relevant clinical characteristics in its presentation, which is evidenced when making comparisons between seminomas and non-seminomas. It was reported that 28% of 254 patients with seminoma and 53% of 168 patients without seminomas in the expression rate of bHCG [33]. A recent German study in more than 400 patients found that in 73% of all non-seminomas, at least the beta or alpha HCG subunit, or both, were elevated, while in seminoma an elevated beta level was present in almost 30% of the cases [34]. The International Germ Cell Cancer Collaborative Group (IGCCCG) even includes chorionic gonadotropin among the criteria of the risk stratification model for metastatic disease, apart from biomarkers such as the primary tumor site, metastatic sites, the amplitude of the Serum α-fetoprotein (AFP), β-chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH) [35]. Equivalent, to a case report carried out in 2017, of a patient with a clinical presentation of hematemesis due to gastric variceal hemorrhage, a mass in the left scrotum that caused the displacement of the penis and the right testicle, where the typical tumor biomarkers and the Serum alpha-fetoprotein levels were 17,090 ng / ml, lactate dehydrogenase was 1,480 U / L, and human chorionic gonadotropin was 287.4 IU / ml [36]. Therefore, there is improvement, thanks to chemotherapy or removal of residual tumors, the levels decrease to the point of becoming undetectable, as in the case of a patient with a testicular tumor with multiple metastases in the lung, retroperitoneal lymph node and brain [37]. Or, failing that, the rate of markers will be significantly higher in stages> CS1, as occurred in a recent report, where the entire cohort of patients presented elevation of bHCG, AFP and LDH, with values of 37.9% 25.6 %, 32.9% and 59.5%, respectively. For greater precision in the bHCG values, in one study they chose to perform a testosterone tolerance test. To in this way discriminate the production of pituitary HCG. Of 60 patients who underwent the administration of testosterone (250 mg), 60% normalized their serum levels of HCG and this was the effective way to consider the elevation of this hormone by the pituitary and not by germ cell tumors. However, other possible biomarkers have been discovered due to epigenetic changes, comprising other than miRNA, DNA methylations, and histone modifications [38]. It has been suggested that microRNA-371a-3p is a sensitive biomarker, which is shown in the comparison made with the usual markers, where miR371 detected CS1 of the seminoma and non-seminoma subtypes with a sensitivity of 87% and 89%, respectively. Unlike AFP and β-hCG, it had sensitivities of 52% and 51% in non-seminomas [39].

Conclusion

Despite the fact that testicular cancer only represents 1% of the types of cancer, it usually occurs at a very early age, causing a deterioration in physical, mental and emotional health, especially in adolescent patients due to its implications in the sexuality and reproduction, for which it is necessary to review the updated clinical guidelines for early detection and thus increase the chances of an effective treatment management and avoid uncontrolled growth that culminates in a metastatic process. The corresponding interventions in the event of a suspected diagnosis are carried out with knowledge of the typical clinical presentation and also encourage promotion and prevention programs through testicular self-examination. An increase in testicular volume without inflammatory signs and in most cases unilateral is indicated in all the check-ups, a situation that indicates the referral to the urologist specialist and the immediate request for alpha-fetoproteins, hCG beta subunit and lactate dehydrogenase, if positive resort to surgical treatment. So far, and according to the review carried out, hCG beta subunit is the usual marker with the highest sensitivity. However, new markers have been reported, which in the future could be useful in the staging and prevention of testicular cancer.

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