

Mature and Immature Teratoma: A Review of Pathological Characteristics and Treatment Options

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Abstract

Testicular teratoma is a sub-type of Non-Seminomatous Germ Cell Tumour (NSGCT) and often occurs in two distinct age groups. Adult testicular teratomas are often mixed and are malignant. Teratoma can be divided histologically into mature and immature. Pure mature teratoma of the testis is rare. Intratubular Germ Cell Neoplasia (ITGCN) is a common feature associated with teratoma. Teratoma is frequently chemoresistant and clinical management of these tumours includes radical inguinal orchidectomy followed by Retroperitoneal Lymph Node (RPLND) dissection if indicated. Long-term oncological outcomes for mature and immature testicular teratoma are equivocal.

Keywords: Testis; Testicular cancer; Teratoma; Mature teratoma; Immature teratoma

Introduction

Testicular teratoma is a sub-type of Non-Seminomatous Germ Cell Tumours (NSGCT) of the testis. Gonadal germ cell tumours (GCT) can be diagnostically challenging for pathologists and correct classification has a major implication on prognosis and therapeutic treatment [1].

Teratoma is a GCT that predominantly occurs in the gonads: the testis and ovaries. They contain well-differentiated or incompletely differentiated elements of at least two germ cells layers (endoderm, ectoderm and/or mesoderm). Mature teratomas are well differentiated relative to the germ cell layers. Immature teratomas are incompletely differentiated and are similar to foetal or embryonic tissue [2]. This article discusses and summaries the pertinent features of mature and immature teratomas of the testis and their significance.

Discussion

Teratomas are the second most common neoplasm in children following yolk sac tumour and occur with a relative frequency ranging from 13 to 19% [3,4]. Two distinctive groups of testicular teratomas occur according to age: pre and post-pubertal. Pure teratomas (non-mixed) are common in the paediatric sub-group, however these are rare in adults. A mixed variant neoplasm is more commonly seen in adults. Mature pre-pubertal teratomas are benign and represent approximately 30% of testicular germ cell tumours in children [5]. Post-pubertal (adult) testicular teratomas are malignant. Malignant testicular teratomas have a higher metastasis rate of 20% as opposed to their ovarian counterparts [6]. Pure teratoma in the testis is rare accounting for 4% of GCT in this organ compared to pure teratoma in 95% of GCTs found in the ovary [1]. As previously mentioned, teratomatous features are more commonly found in mixed GCTs in the testis, rather than pure teratoma, and are apparent in approximately 50% of these tumours [1].

Clinical presentation and diagnosis

Clinical presentation of teratoma is similar to other neoplasms of the testis. Teratoma, both mature and immature, often present clinically as a painful testicular mass [7]. The presenting symptom of testicular pain can be attributed to haemorrhage and haematoma formation and thus the pressure applied to the testicle during tumour formation [8]. Teratomas are renowned for their rapid growth and highly vasculitic nature compared to seminoma. These tumours are often discovered incidentally or indirectly during the assessment of testicular trauma as

an initial presenting complaint. They can be present for some time prior to detection, as is the case with most testicular masses.

Examination findings for teratoma are usually consistent with those for a suspected testicular neoplasm. On examination atrophy of the affected or contralateral testis is common and a palpable firm mass within the testis is suggestive of malignancy. An associated hydrocele may be present. For teratomas, which cannot be distinguished clinically from other tumours, the patient workup should be the same as would be for the evaluation of any other suspicious testicular masses. Thorough abdominal examination specifically for masses or tenderness, inguinal and supraclavicular lymphadenopathy, gynecomastia and chest auscultation for evidence of metastatic disease should be performed [9].

Both mature and immature teratomas are generally associated with normal testicular tumour markers: Beta Human Chorionic Gonadotropin (B-hCG) and Alpha Feto-Protein (aFP). Occasionally some exhibit mildly elevated aFP levels. On sonographic evaluation, teratomas typically demonstrate the appearance of cystic areas with intervening septa and solid areas. The presence of calcifications in the tumour is another helpful sonographic finding associated with teratomas, however, diagnosis can only be confirmed by pathologic evaluation [4]. To evaluate for metastatic disease a staging CT thorax and abdomen is recommended in all cases of testicular cancer [7]. Up to 10% of patients present with subpleural nodes, which are not detectable by conventional chest radiograph [8]. There is no evidence for fluorodeoxyglucose-PET (FDG-PET) imaging in the staging of testicular cancer [9].

Genetics of testicular teratomas

Pre-pubertal teratomas are diploid, often lack chromosomal

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Received November 13, 2013; **Accepted** January 27, 2014; **Published** January 29, 2014

Citation: Wetherell D, Weerakoon M, Williams D, Beharry BK, Sliwinski A, et al. (2014) Mature and Immature Teratoma: A Review of Pathological Characteristics and Treatment Options. Med Surg Urol 3: 124. doi:10.4172/2168-9857.1000124

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imbalances and do not exhibit isochromosome formation (i(12p)) [10,11]. In contrast, adult teratomas, most of which are mixed type, are hypotriploid and are associated with chromosomal abnormalities. A pertinent genetic feature of testicular GCTs is the acquisition and over representation of 12p sequences. Gain of one or more of these genes on 12p is crucial in the development of testicular GCTs [12]. Other genetic changes found in a quarter of these tumours include: partial loss of chromosome 13 (particularly q31) and gain of chromosome 7 (particularly q11), chromosome 8 and the X chromosome [13].

Macroscopic and microscopic features

Mature post-pubertal teratomas have a macroscopic appearance of solid testicular tumours. Microscopically mature teratomas have a disordered arrangement and demonstrate cytological atypia [1]. Adjacent seminiferous tubules often display carcinoma in situ or intratubular germ cell neoplasia (ITGCN) in up to 90%, which is associated with malignant potential. Pre-pubertal teratomas, which are benign tumours, are seldom associated with ITGCN. There is frequently widespread testicular atrophy and absent spermatogenesis [14]. As teratomas are germ cell tumours they can host a variety of non-tumour native tissues. For instance, in mature ovarian teratomas choroid plexus, thyroid and pituitary tissue can be present, with the latter manifesting systemically as prolactinomas [15]. In mature testicular tumours however, this non-tumour native tissue is seen less frequently.

Pure adult testicular teratomas are rare and around a third are mixed GCTs. The occurrence of mixed teratoma GCTs can be attributed to the pathogenesis whereby malignant germ cells (ITGCN) differentiate into non-teratomatous cells prior to the formation of teratomatous elements [1]. This accounts for the association of ITGCN seen in pure teratomas, as well as metastases of non-teratomatous cell types.

The diagnosis of immaturity for a teratoma requires tissue resembling embryonic origin, in particular the appearance of neuroepithelium [1]. However, the presence of this tissue or 'immaturity' of a post-pubertal testicular teratoma is not significant. Some pathologists believe that the teratomas should not be classified as mature or immature due to them having the same genetic changes and biological potential, in both pre and post-pubertal populations [15]. As mentioned previously, the pathogenesis of testicular teratoma is that malignant transformation occurs prior to teratomatous differentiation. Hence the further immature differentiation of teratomatous tissue is irrelevant, as the malignant process has occurred earlier [1].

Primitive Neuro ectodermal Tumour (PNET) is diagnosed in the presence of an overgrowth of immature neural elements in teratomas [1]. Extra testicular PNETs from GCTs as a result of metastatic spread are frequently resistant to chemotherapy and are associated with a high rate of mortality [16]. Despite testicular teratomas having malignant behaviour in the absence of excess neural tissue (i.e. PNET), the presence of this tissue does have a negative prognostic value [1].

Associated tumours: dermoid and epidermoid cysts

Testicular dermoid cysts are rare lesions and whether these should be classed as a variant of mature teratoma is still under discussion [17]. Epidermoid cysts represent 1% of all testicular tumours but whether they are true neoplasms still remains a topic of debate [18]. Testicular dermoid cysts are synonymous with the features of ovarian dermoid cysts. Their macroscopic appearance is of a cystic tumour often containing grossly identifiable hair [19]. In contrast to mature post-pubertal teratomas, these lesions often occur in a testis with normal spermatogenesis and lack of atrophy. They lack adjacent ITGCN and

cytological atypia, which are microscopic features of mature post-pubertal teratomas [18]. Lipogranulomatous reaction in the testicular parenchyma and pilosebaceous cyst arrangement is diagnostically characteristic of testicular dermoid cysts [1]. Epidermoid cysts are similarly not associated with ITGCN and lack atypia and mitotic activity [14] (Figures 1-3).

Treatment and Outcomes

Low- stage (Stage I)

Only 2 to 6% of NSCGT consist of pure teratoma in adults. As previously discussed, mature pre-pubertal teratoma has a benign clinical course, however in adults metastases for both mature and immature teratoma have been reported in 13 to 60% of cases at initial presentation [4,19,20]. The standard treatment for all testicular tumours (GCTs) in adults is radical inguinal orchidectomy. Retroperitoneal metastasis has been identified in approximately 20 to 30% of patients with clinical stage I pure testicular teratoma treated with primary Retroperitoneal Lymph Node Dissection (RPLND) [6,20]. However, RPLND is still controversial in patients with clinical stage I pure teratoma. The adjuvant treatment options remain RPLND or surveillance, however as previously stated around a quarter of these patients will have retroperitoneal metastasis and increased to 75% for patients with clinical stage IIA disease. The teratomatous component of GCTs is particularly resistant to chemotherapy, which is often an

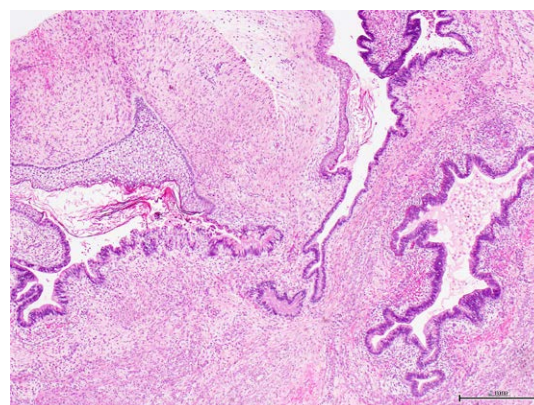


Figure 1: Mature teratoma (H&E, 40x) showing squamous epithelium (left upper) and enteric glandular epithelium (bottom right).

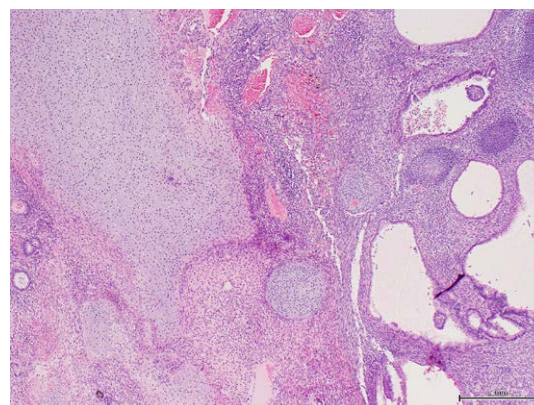


Figure 2: Mixed mature (right) and immature (left) teratoma (H&E 40x), including nodules of immature cartilage (centre, bottom and left).

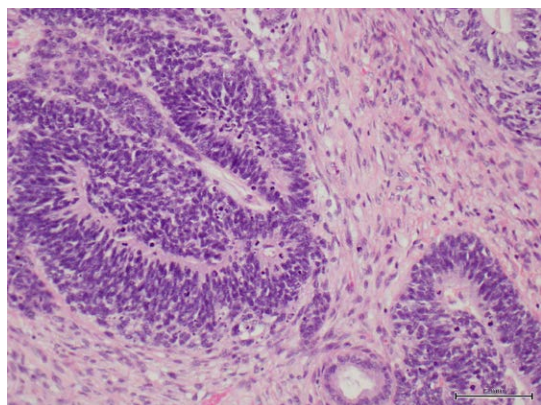


Figure 3: Immature teratoma (H&E 200x) showing immature neuroepithelium (left side).

adjuvant treatment option used following RPLND for other viable NSGCT elements [21].

Advanced stage (Stage IIA/B)

Almost two thirds of men with NSGCT's, which include pure teratoma, present with advanced metastatic disease. This particular group of men often has regression of other NSGCT elements in the testis. Tumour markers may be elevated in this sub group and the presence of other GCT's such as yolk sac or embryonal sac carcinoma are often present in metastasised sites [6]. Treatment is entirely dependent upon histology of primary tumour and the prognosis as defined as per the International Germ Cell Consensus Classification guidelines (IGCCCG), which is based on 5202 non-seminomatous cases [22]. There is a general consensus that patients with advanced stage NSGCT can be managed with chemotherapy except for stage II NSGCT disease without elevated tumour markers; this subgroup can be alternatively treated with RPLND or surveillance. If surveillance is chosen, patients should be scheduled for review six weeks post-diagnosis specifically looking for disease progression. Growth of the lesion without a respective raise in tumour markers suggests teratoma or other malignant transformation and RPLND is highly recommended [7]. If tumour markers are also raised, then chemotherapy is the initial indication; with PEB (cisplatin, etoposide, bleomycin) being the chemotherapy of choice as per the IGCCCG guidelines [7,23,24]. Patients refusing to undergo primary chemotherapy may have RPLND with adjuvant PEB (2 cycles) in the case of metastatic disease. The outcomes post RPLND and chemotherapy are equivocal with 98% cure rate [6]. The side effects of either treatment are different, thus extensive discussion needs to be taken between patient and clinician with regards to treatment options.

Seminomas are radiosensitive hence Radiotherapy (RT) is an effective treatment for stage I and IIA-B disease. However, RT is not recommended for the treatment of NSGCTs. These tumours, including mature and immature teratoma, are often mixed cell type therefore chemotherapy is required to kill the chemosensitive components in combination with surgical excision of residual mass (e.g. teratoma) [25].

Advanced stage (Stage IIC and III)

Around 37% of patients with pure teratoma present with advanced disease [20]. All advanced (stage III) NSGCTs, including mature and immature teratoma, should be assessed and stratified on a clinical

basis into either favourable-risk or intermediate/poor risk group. Recommended treatment for the favourable risk group is at least three cycles of adjuvant chemotherapy (PEB). These patients should all undergo restaging following primary chemotherapy and if there is complete remission resection is not indicated [26]. The extent of resection of residual masses (e.g. RPLND or wedge lung resection) should also take into account individual patient and quality of life factors [7]. The histological diagnosis should not influence the treatment course in stage III disease and in general all advanced stage NSGCTs, including pure teratoma, should be treated according to the same pathway as described above [7,20].

The Impact of teratoma in Mixed NSGCTs

Teratoma in adults frequently presents as a mixed type tumour, with yolk sac or embryonal sac tumour in 50% of cases [6]. The impact of teratomatous elements in orchidectomy specimens has been investigated to detail. Currently, evidence shows a correlation between teratoma within the orchidectomy specimen with an increased likelihood of teratoma in the post chemotherapy RPLND specimen with a current rate of 20% of teratomatous elements found in primary RPLND and 40% of teratomatous elements in patients undergoing RPLND post chemotherapy [19-21]. On the contrary, the absence of teratoma in the retroperitoneum is not suggested if teratoma is not present in the orchidectomy specimen [6,21].

Mature teratoma is found in approximately 35 to 40% of primary chemotherapy RPLND (PC-RPLND) specimens for advanced NSGCT [27]. One study by Steyerberg et al. analysed 556 RPLND specimens post-chemotherapy for NSGCTs and found mature teratoma in 42% and that a teratoma negative primary tumour was a strong predictor of necrosis in the PC-RPLND specimen [28]. Currently there is no imaging modality that accurately distinguish between necrosis, viable cancer or teratoma in patients treated with chemotherapy for NSGCTs [29].

Retroperitoneal teratoma in NSGCT treated with primary chemotherapy (<1 cm)

Serologic and radiographic complete response to first line chemotherapy (defined as a residual transverse axial lesion on CT less than 1 cm) is achieved in 26 to 64% of patients with advanced NSGCT [27]. These patients are considered to be in a low-risk group, however, some centers still recommend RPLND following primary chemotherapy from a rationale that radiographic estimation of the size of residual nodal tissue following primary chemotherapy is unreliable. This remains a controversial topic and in particular the lack of imaging criteria and consensus on nodal size criteria [27]. A study by Oldenburg et al. of 87 RPLND patients post-chemotherapy showed that 30% with lymph nodes <1 cm had viable tumour present (20% teratoma and 10% malignant tumour) [30]. The European Germ Cell Cancer Consensus group and recent literature recommends that patients who achieve remission, defined as residual retroperitoneal lesion <1 cm, can be safely observed [31-34].

Retroperitoneal teratoma in NSGCT treated with primary chemotherapy (>1 cm)

Retroperitoneal lymph-node dissection should be performed for radiographic masses >1cm post-chemotherapy for NSGCTs [27]. Loehrer et al. reported on 51 patients who had surgical resections of teratoma after cisplatin-based chemotherapy. In this study twenty patients (39%) experienced relapse with either histologically proven teratoma (10 patients) or viable GCT (10 patients) [35]. Sonneveld

et al. reported on 51 patients with retroperitoneal teratoma after chemotherapy for NSGCT [36]. In their series, nine patients experienced a relapse, with growing mature teratoma in 56%, teratoma with malignant transformation in 33%, and viable GCT in 11%. Another contemporary cohort of 210 patients by Carver et al. with only pure teratomatous elements at post chemotherapy RPLND revealed mature teratoma in 178 patients (85%), immature teratoma in 15 patients (7%) and teratoma with malignant transformation in 17 patients (8%) [21]. Of the 193 patients with mature or immature teratoma, 24 patients (12%) experienced relapse after post chemotherapy RPLND and two patients experienced relapse with teratoma with malignant transformation. For men relapsing with only teratomatous histology, the most common sites of relapse were retro-crural and pulmonary in seven and four patients respectively. Other recurrence sites include liver, pelvis, neck and para-aortic [21]. Patients with teratoma with malignant transformation are known to have a poorer prognosis and attempted resection of the primary site of recurrence remains the treatment of choice due to the poor sensitivity of these tumours to chemotherapy [21].

Oncological outcomes

As previously discussed, the oncological outcomes for teratoma pre and post chemotherapy RPLND are determined by the IGCCCG staging and grading of severity. Significant predictors for increased risk of disease recurrence include higher pre and post chemotherapy nodal size, intermediate or poor IGCCCG risk classification and evidence of malignant transformation [21]. Of particular note, histological findings of immature teratoma, when compared to mature teratoma did not increase the risk of disease recurrence [37]. However, mature teratoma in the PC-RPLND specimen is commonly associated with late relapse [36,38]. Overall, the oncological outcomes for immature and mature teratoma remain equivocal as per IGCCCG staging and degree of severity.

Conclusion

In adults mixed GCTs with teratomatous elements are more common than pure teratoma. Mature and immature teratomas in the post-pubertal setting and often exhibit malignant behavior. Distinction between mature and immature teratoma is made histologically, with the latter closely resembling foetal or embryonic tissue. The biological behaviour of immature teratoma is identical to that of mature teratoma. RPLND for patients with clinical stage I pure teratoma is still controversial. Treatment of metastatic testicular teratomas is complex but is often primary chemotherapy followed by RPLND or surveillance and is guided clinically. However, teratomas are resistant and therefore often respond poorly to chemotherapy. Long-term oncological outcomes are equivocal for both mature and immature teratoma.

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