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Journal of Endocrinology and Disorders

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Open Access

Review Article

Terato-Neuroendocrine Tumour of Testis: Review and Update

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Received Date: 22 November 2023 | **Accepted Date:** 11 December 2023 | **Published Date:** 18 January 2024

Citation: Anthony Kodzo-Grey Venyo, (2024), Terato-Neuroendocrine Tumour of Testis: Review and Update, *J. Endocrinology and Disorders*, 8(1): **DOI:10.31579/2640-1045/164**

Abstract

Neuro-endocrine tumours commonly emanate from intestinal and respiratory epithelium. Neuro-endocrine tumours could also on rare occasions afflict various organs of the human body. Neuro-endocrine tumour afflicting the testis is an uncommon tumour which does account for far less than one percent (<1%) of all tumours of testis. To the knowledge of the author, less than 100 cases of primary neuro-endocrine tumour of the testis had been reported so far in the global literature. The reported cases of neuro-endocrine tumour of testis have ranged between 10 years and 83 years of age and the reported incidence rate had been noted to be higher within the fifth and sixth decade of life. Majority of patients who are afflicted by neuro-endocrine tumour of testis do tend to manifest with unilateral painless testicular mass. Sixteen percent (16%) of patients who are afflicted by neuro-endocrine tumour of testis do manifest with symptoms of neuroendocrine tumour syndrome. Eleven percent (11%) of primary neuroendocrine tumours of testis tend to be diagnosed initially with a contemporaneously-associated metastasis. Neuro-endocrine tumours of the testis occur as a primary testicular neuroendocrine tumour, or they may be metastatic neuroendocrine tumour to the testis with the primary tumour originating from elsewhere in the body especially from the gastrointestinal or cardiorespiratory tract system. Primary neuro-endocrine tumour of testis, could be further sub-divided into: (a) primary pure neuroendocrine tumour of testis; and (b) neuro-endocrine tumour of testis contemporaneously associated with teratoma or dermoid/epidermoid cysts. Once a neuro-endocrine tumour of testis is diagnosed, it is pivotal that clinicians should exclude a metastatic neuroendocrine tumour to the testis with the primary tumour originating from elsewhere within the human body. It has been iterated that the presence of teratomas elements within the neuro-endocrine tumour of testis does sufficiently rule out the primary site outside the testis. In order to accurately diagnose the neuro-endocrine tumour of the testis, it has been advised that it is pertinent to submit the tumour mass entirely and to look for any additional lineage of differentiation. Twenty five percent of primary neuro-endocrine tumours of testis are associated with teratoma. Histogenesis of pure neuroendocrine tumour of the testis is yet to be clarified. Two postulates had been propounded in relation to the mode origin of neuroendocrine tumour of testis including: (1) Emanation from a teratoma which is the germ cell origin postulate; (2) Emanating from argentaffin cells that are located within crypts of Lieberkühn .A study related to three pure testicular neuroendocrine tumours of testis had indicated that pure neuroendocrine tumour of testis might have different genetic background other than germ cell tumour.[11] Histopathology examination of specimens of neuro-endocrine tumour of testis has tended to demonstrate tumour cells that tend to be typified by the presence of nests of small round cells with uniform nuclei forming small acini and rosettes or sheets. The cells tend to contain eosinophilic granules within the cytoplasm and granular chromatin within the nuclei. The tumour cells do exhibit positive staining for neuroendocrine markers like chromogranin and synaptophysin as illustrated in detail in the article. Radical orchidectomy is the most adopted option of treatment; nevertheless, necessitation for the undertaking of provision of adjuvant treatment depending upon histological grading has not been clarified. Because of the possibility of development of local recurrence and or distant metastases after a long time, it is pivotal for all clinicians to carefully follow-up their patients over a long-period of time with clinical, laboratory testing and radiology-imaging testing follow-ups in order to establish early diagnosis of any local recurrence or distant metastasis to be able provide further treatment of curative intent early. There is also the possibility that neuro-endocrine tumours of testis had so far been under-reported due to mis diagnosis of the tumour upon pathology examination of the testicular tumour or the correct set of monoclonal and polyclonal antibodies had not been utilized in the immunohistochemistry study assessment of the tumours. It would be advised that all clinicians and pathologists globally should have a high index of suspicion for a neuro-endocrine tumour of testis in order to establish prompt diagnosis of the tumour and to provide appropriate assessment, treatment and follow-up of all their patients.

Key words: neuro-endocrine tumour of testis; carcinoid tumour of testis; testicular carcinoid tumour; histopathology; immunohistochemistry; orchidectomy; recurrence; carcinoid syndrome

Introduction

Neuro-endocrine tumours often tend to be sporadically encountered within t he gastrointestinal tract system originating from embryonal gastrointestinal tract and at times within the respiratory tract. [1] However, on extremely rar e occasions, neuroendocrine tumours could be found primarily origination f rom various organs of the human body. Primary or metastatic neuroendocri ne tumour on exceedingly rare occasions could afflict the testis. The cell of origin of primary neuroendocrine tumour of the testis has not been clarified up to date.[1] Considering the rarity of both primary and metastatic neuroen docrine tumour of testis, it would be envisaged that majority of clinicians al l over the world not have encountered a case of neuro-endocrine tumour of t estis before and they would also tend not to be familiar with the manifestati ons, diagnostic features, management as well as outcome of patients who ar e afflicted by neuro-endocrine tumour of testis. The ensuing article on neuro -endocrine tumour of testis is divided into two parts: (A) Overview which h as discussed miscellaneous general aspects of neuro-endocrine tumours, and (B) Miscellaneous narrations and discussions from some case reports, case s eries, and studies related to neuro-endocrine tumour of testis.

Aim

To review and update the literature on neuro-endocrine tumour of testis.

Methods

Internet data bases were searched including: Google; Google Scholar; Yaho o; and PUBMED. The search words that were used included: Neuroendocri ne tumour of testis; Testicular neuroendocrine tumour; Testicular Carcinoid Tumour; Carcinoid tumour of testis. Thirty- eight (38) references were iden tified which were used to write the article which has been divided into two p arts: A) Overview which has discussed miscellaneous general aspects of ne uro-endocrine tumours, and (B) Miscellaneous narrations and discussions fr om some case reports, case series, and studies related to neuro-endocrine tu mour of testis.

Results

[a] overview

Definition / general statement [2]

- It has been iterated that Teratoma-neuroendocrine tumour of the testis is a well differentiated neuroendocrine tumour (NET) that is a low-grade epithelial neoplasm with neuroendocrine differentiation

Essential features [2]

- It has been pointed out that primary testicular NETs could be either pure tumours that tend to account for 75% of the tumours or the tumours could be associated with teratoma which does occur in 25% of NETs of the testis.
- It has been documented that NETs of testis demonstrate an insular or trabecular growth pattern with salt and pepper nuclear chromatin pattern
- It has been pointed out that majority of NETs of testis are not associated with isochromosome 12p or germ cell neoplasia in situ (GCNIS)

Terminology [2]

- It has been pointed out that Teratoma-neuroendocrine tumour of the testis is also referred to as pure NET, testicular NET, prepubertal type or post-pubertal type or mono-dermal teratoma of the testis.
- It has been advised that the terminologies which are not recommended to be used include: carcinoid tumour of testis, atypical carcinoid tumour of testis, and neuroendocrine carcinoma of testis

Epidemiology [2]

- It has been pointed out that Teratoma-neuroendocrine tumour of testis is very rare, and this accounts for less than one percent (< 1%) of all testicular neoplasms [3]
- It has been iterated that teratoma-neuroendocrine tumour is more commonly encountered in ovaries than within testes (15:1)
- It has been documented that the mean age at presentation of teratoma-neuro-endocrine tumour of testis is 46 years and the ages of patients who had been documented to be afflicted with Teratoma-neuroendocrine tumour of testis has ranged between 10 years and 83 years
- It has been documented that majority of cases of teratoma-neuroendocrine tumour of testis had been reported in Europe and the United States of America. with fewer cases reported from Asia and Africa
- It had also been documented that metastatic neuroendocrine tumour to the testis from other sites including the lung or gastrointestinal tract had been reported in the global literature

Sites

- It has also been pointed out that NET within the genitourinary tract is rare and could occur within the kidney, urinary bladder, prostate gland, the testis or urethra [2]

Pathophysiology [2]

- It has been iterated that teratoma-neuroendocrine tumour of testis does arise within the setting of prepubertal teratoma (testicular NET, prepubertal type)
- It has been pointed out that 75% of teratoma-neuroendocrine tumours of testis do occur as pure NET, with the remaining 25% of tumours occurring with other teratomatous components including dermoid cysts and epidermoid cysts. [3] [4] [5]
- It has been documented that majority of teratoma-neuroendocrine tumours of testes are not associated with GCNIS or isochromosome 12p
- It has in addition been pointed out that rare cases of post-pubertal type testicular NET had been reported in the global literature. [6]

Aetiology

- It has been iterated that the aetiology of teratoma-neuroendocrine tumour of testis is not known [2]

Clinical features [2]

- It has been iterated that most commonly teratoma-neuroendocrine tumour of testis manifests as a testicular mass or swelling, which might or may not be associated with testicular pain
- It has been documented that bilateral involvement of teratoma-neuroendocrine tumour of testis is no commonly encountered and the association with cryptorchidism is also rare
- It has been pointed out that 10% of cases of teratoma-neuroendocrine tumour of testis does occur in association with hydrocele [5]

- It has been iterated that clinical carcinoid syndrome including manifestation with hot flashes, diarrhoea and palpitations had been reported in 7% to 12% of cases of teratoma-neuroendocrine tumour of testis. [3]
- It has been explained that in cases of teratoma-neuroendocrine tumour of testis, metastases do occur by means of hematogenous spread to the lungs, liver, bones, soft tissue, skin, heart as well as contralateral testis; nevertheless, lymphatic spread had also been observed.

Laboratory tests

Routine urine tests

- Urinalysis, urine microscopy and culture end to be undertaken in the initial assessment of patients who manifest with testicular mass as part of the general initial assessment of patients but generally the results with tend to be normal but if there is any urinary tract infection, it would be treated appropriately based upon the antibiotic sensitivity pattern of the cultured organism to improve the general condition of the patient.

Haematology blood tests

- Routine haematology tests tend to be undertaken in the initial assessment of patients who manifest with testicular mass including full blood count and INR as part of the general initial assessment of patients but generally the results with tend to be normal but if any abnormality is found, it would be investigated and treated to improve the general condition of the patient.

Biochemistry tests including blood and urine tests

- CRP, Serum urea and electrolytes, liver function tests, bone profile and random blood glucose are general tests that tend to be undertaken in the general assessment of patients who manifest with lump or mass in the testis and generally in majority of patients the results would tend to be normal but if any abnormality is detected it would be investigated appropriately and treated to improve the general condition of the patient.
- In the assessment of patients who manifest with testicular mass / tumour, serum tumour marker levels including Beta Human Chorionic Gonadotrophin (BHCG), Lactate Dehydrogenase (LDH) and Alpha Feto protein (AFP) levels tend to be undertaken as part of the initial assessment of patients and most often the results would tend to be normal.
- When carcinoid syndrome is suspected, a number of urine and blood tests tend to be undertaken as part of patient assessment including:
  - ❖ Measurement of biogenic amines levels, including: serotonin, 5-HT, catecholamines, histamine) and its metabolites in the platelets, plasma, and urine of patients can be helpful in diagnosis.
  - ❖ Urinary 5-HIAA levels are usually increased and aid in the assessment of carcinoid tumours. Measurement of urinary 5-HIAA levels can help in diagnosing carcinoid syndrome but may not help in detecting tumours at an early stage of development when they are potentially curable with resection.
  - ❖ Although the detection of urinary 5-HIAA is the single best screening method for carcinoid tumours, the level is not always raised and the measurement of other peptides including: SP, neuropeptide K, chromogranin, might be necessary for the diagnosis and follow-up.
  - ❖ Fasting plasma 5-HIAA assay is a more stable and useful test in comparison with whole-blood serotonin assay and it is more convenient than 24-hour urine collection.
  - ❖ In a study, CDX2 was highly concluded to be indicative of GI carcinoid tumour, whilst TTF-1 had high specificity for pulmonary tumours.[1] One (17%) of 6 gastric carcinoids stained with CDX2, whereas 8 (53%) of 15 pulmonary carcinoids stained with TTF-1. None of the GI tumours stained with TTF-1.
  - ❖ Multi-disciplinary team discussion would help every clinician or urologist who is suspecting neuroendocrine tumour of testis to decide on the best biochemistry tests to undertake in the initial assessment of their patients who are suspected to have neuroendocrine tumour of testis

Radiology Imaging

Various types of radiology imaging could be utilized during the initial and follow up assessments and follow-up assessments of patients who have neuroendocrine tumour of testis and some of these include:

- Ultrasound scan of testes, abdomen and pelvis.
- Computed tomography (CT) scan of thorax, abdomen and pelvis and testes and scrotal contents.
- Magnetic Resonance Imaging (MRI) scan of thorax, abdomen and pelvis and testes and scrotal contents.
- Bone scan
- PET / CT scan
- Others which tend to be recommended by the multi-disciplinary team

Diagnosis

- It has been pointed out that the diagnosis of testicular NET is made based upon histology examination features of the surgical resection specimen of the testis.

Prognostic factors

- It has been documented that primary testicular NET associated with testicular teratoma does seem to portend a better prognosis than pure NET
- It has been iterated that metastatic disease is associated with atypical features, including larger tumour size measuring greater than 7 cm (> 7 cm), increased mitotic activity and carcinoid syndrome [3] [5]

Treatment [2]

- It has been iterated that the treatment of teratoma-neuroendocrine tumour of testis entails the undertaking of orchidectomy
- It has in addition been documented that within a metastatic setting, retroperitoneal lymph node dissection and receptor targeted radiotherapy may be utilised; nevertheless, chemotherapy and radiotherapy had been reported to be associated with minimal benefits

Gross description [2]

- It has been iterated that macroscopy examination of specimens of teratoma-neuroendocrine tumour of testis does demonstrate well circumscribed, solid, yellow-tan to brown tumour of testis that ranges in size from 0.5 cm up to 11 cm [5]
- It has been iterated that macroscopy examination of specimens of teratoma-neuroendocrine tumour of testis does demonstrate cystic changes or calcifications that could be visualised in association with teratoma component
- It has also been pointed out that in teratoma-neuroendocrine tumour of testis, extra-testicular growth with involvement of spermatic cord does occur uncommonly **[5]**

Microscopic (histologic) description [2]

The ensuing summations had been made regarding microscopy histopathology examination findings on cases of teratoma-neuroendocrine tumour of testis:

- Growth pattern
    - ❖ It has been iterated that microscopy examination of specimens of teratoma-neuroendocrine tumour of testis does tend to demonstrate mostly solid nests, insular or trabecular growth patterns
    - ❖ It has been iterated that microscopy examination of specimens of teratoma-neuroendocrine tumour of testis does tend to demonstrate acinar and glandular growth pattern with luminal mucin admixed with other growth patterns may be seen, [3] [6]
- Stroma
    - ❖ It has been iterated that microscopy examination of specimens of teratoma-neuroendocrine tumour of testis does tend to demonstrate the stroma depicting delicate fibrous or hyalinized stroma [7]
    - ❖ It has been iterated that microscopy examination of specimens of teratoma-neuroendocrine tumour of testis does tend to demonstrate the tumour cells depicting monomorphic with abundant granular eosinophilic to pale cytoplasm
    - ❖ It has been iterated that microscopy examination of specimens of teratoma-neuroendocrine tumour of testis does tend to demonstrate uniform round nuclei with fine or salt and pepper chromatin [3]
- It has been iterated that microscopy examination of specimens of teratoma-neuroendocrine tumour of testis does tend to demonstrate that majority of cases tend to be un-associated with GCNIS [3]
- It has been iterated that microscopy examination of specimens of teratoma-neuroendocrine tumour of testis does tend to demonstrate mitotic figures, necrosis and vascular invasion which are infrequently visualised [3]
- Atypical features that tend to be visualised in cases of teratoma-neuroendocrine tumour of testis include necrosis, nuclear atypia and > 2 mitoses per 10 high power fields (HPF) [3] [8]

Cytology description [2]

- It has been iterated that cytology examination of specimens of teratoma-neuroendocrine tumour of testis does tend to demonstrate isolated or sheets of neoplastic cells with granular cytoplasm, uniform round nuclei and uniformly distributed fine nuclear chromatin

Immunohistochemistry staining studies

Positive stains [2]

It had been iterated that immunohistochemistry staining studies of specimens of teratoma-neuroendocrine tumour of testis does tend to demonstrate positive staining for the ensuing tumour markers which tend to be mostly positive:

- Cytokeratin
- Synaptophysin
- Chromogranin A
- CD56 [5] [9]

It had also been iterated that immunohistochemistry staining examination of specimens of teratoma-neuroendocrine tumour of testis does tend to demonstrate positive staining for the ensuing tumour markers which tend to be less frequency expressed:

- Substance P,
- Gastrin
- VIP
- Neurofilaments. [10]

Negative stains [2]

It had also been iterated that immunohistochemistry staining examination of specimens of teratoma-neuroendocrine tumour of testis does tend to demonstrate negative staining for the ensuing tumour markers: [2]

- OCT ¾
- CD30
- KIT
- TTTF1
- SF1
- SOX2
- Alpha inhibin
- And CDX2. [6]

Electron microscopy description

It had also been iterated that electron microscopy examination of specimens of teratoma-neuroendocrine tumour of testis does tend to demonstrate the ensuing [2]

- Pleomorphic to more regular round to oval neurosecretory granules

Molecular / cytogenetics description

The molecular and cytogenetics features of teratoma-neuroendocrine tumours of the testes had been summated to include the ensuing: [2]

- DNA ploidy studies do demonstrate a near diploid profile [5]
- As most cases of teratoma-neuroendocrine tumour of testis are not associated with GCNIS, they do not show isochromosome 12p or numerical aberrations in the X chromosome, which are commonly visualised in GCNIS derived germ cell tumours
    - ❖ In rare cases, assessment of isochromosome 12p might be indicated if the post-pubertal type of teratoma-neuroendocrine tumour is suspected

Differential diagnosis

The differential diagnoses of teratoma-neuroendocrine tumour of testis had been summated to include the ensuing: [2]

- Metastatic neuroendocrine tumour of testis.:
    - ❖ It has been stated that usually metastatic neuroendocrine tumour primary the primary tumour elsewhere metastasizing to the testis, usually manifests with bilateral involvement of the testis, multifocality, vascular invasion aa well as extra-testicular localization
- Sertoli cell tumour of testis:

- ❖ It has been pointed out that Sertoli cell tumour of testis lacks prominent cytoplasmic granularity and salt and pepper pattern of nuclear chromatin
- ❖ It has been pointed out that Sertoli cell tumour of testis does exhibit positive immunohistochemistry expression for the ensuing tumour markers:
  - Alpha inhibin
  - Calretinin
  - SF1
  - And beta catenin (nuclear)
  - And sometimes Chromogranin and synaptophysin.

- Granuloma cell tumour of testis.
  - ❖ It has been pointed out that the neoplastic cells in Granuloma cell tumour do contain scant cytoplasm, elongated nuclei with nuclear grooves
  - ❖ It has been pointed out that in Granuloma cell tumour of testis, there is no immunohistochemistry expression of:
    - synaptophysin or
    - chromogranin.

[B] Miscellaneous Narrations and Discussions from Some Case Reports, Case Series, and Studies Related to Neuroendocrine Tumours of Testis.

Ordóñez et al. [10] examined a primary pure testicular carcinoid from a 48-year-old man with antisera raised against various neurohormonal polypeptides. Immunohistochemistry staining studies of the tumour demonstrated that both argyrophil and argentaffin reactions were positive. The immunohistochemical finding of immunoreactive cells for 5-hydroxytryptamine (5-HT) (serotonin), substance P, and vasoactive intestinal polypeptide (VIP) also demonstrated the multihormonal nature of this tumour.

Widmeier et al. [11] stated the following:

- Neuroendocrine cells could cause various types of malignancies throughout the human body which is known as the neuroendocrine tumours (NETs) or carcinoid tumours.
- The primary testicular carcinoid tumour (PTCT) does account for less than 1% of the testicular tumours and for only 0.2% of all carcinoid tumours which represents already a very rare tumour.
- They were reporting a patient who had a history of an exceptionally rare primary testicular carcinoid tumour, which had exhibited positive staining for Cdx-2 along with a literature review.

Widmeier et al. [11] reported a 44-year-old patient who did not have any significant past medical history and who was diagnosed in September 2009 with primary testicular carcinoid tumour, which was surprisingly staining positively for Cdx-2, too. At the time of the initial diagnosis the tumour, the tumour was identified to have already shown histopathological infiltration of veins. DOTA-TATE-PET/CT radiology imaging and endoscopy studies did not demonstrate any signs of distant metastases and in particular no gastrointestinal manifestation following no further medical indication for systemic chemotherapy. Widmeier et al. [11] also reported that the continuous and close follow-up of the patient had reached a total of over 10 years at the time of publication and the patient had remained in complete remission.

Widmejer et al. [11] made the ensuing conclusions:

- The diagnosis of primary testicular carcinoid is based upon histopathology examination of the testicular tumour.
- The detailed histopathology assessment of biomarkers based upon immunohistochemistry is very important for the classification and the prognosis of the primary testicular carcinoid tumour.
- Primary testicular carcinoid tumour with Cdx-2 positive stain outlined an exceptionally uncommon neoplastic entity without a consensus about general follow-up guidelines, that requires close clinical and imaging aftercare and consideration in Cdx-2 positive metastatic tumour of unknown origin.

Takada et al. [12] stated the following:

- Primary testicular carcinoid tumours (TCT) are very rare neoplasms, and a large tumour size and the presence of carcinoid syndrome predict a malignant course.
- Histologically, it is difficult to differentiate between benign and malignant TCTs.

Takada et al. [12] reported a case of a primary pure TCT with an unusual manifestation in a 23- year-old man, who had an asymptomatic, enlarged scrotum on the right side for 7 years. On macroscopy examination, the tumour had measured 9.6 cm in diameter. The Ki-67 labelling index of the tumour was 19.8%. High inguinal orchidectomy was undertaken, and 30 months after his surgery the patient remained asymptomatic.

Darré et al. [7] stated that primary carcinoid tumours are rare and constitute 0.23% of all testicular tumours. Darré et al. [7] reported a case of primary carcinoid tumour of testicular localization, with a review of the literature. Darré et al. [7] reported a 29-year-old man, who did not have any specific ascendants, who had manifested to the urology department for progressive scrotal swelling of 6 months, that was associated with pain. After he had undergone orchidectomy surgery, histology examination of the testicular tumour demonstrated diffuse tumour proliferation which was composed of small round monotone cells with hyperchromatic nuclei evoking undifferentiated carcinoma. Immunohistochemistry staining studies of the tumour demonstrated that the tumour cells had exhibited positive staining for chromogranin A and negative staining for placental alkaline phosphatase and α-fetoprotein. Darré et al. [7] made the ensuing conclusions:

- Primary neuroendocrine carcinoma of the testis is a very uncommon malignant tumour.
- Immunohistochemistry staining study of the tumour contributes to its diagnosis in relation to other metastatic neuroendocrine carcinomas, carcinoid tumour teratomas, seminoma, and Sertoli cells.

Chikkaraddi et al. [13] stated that primary carcinoid tumours of the testis are very rare, and they seldom manifest with carcinoid syndrome. Chikkaraddi et al. [13] reported a hereto unreported instance, where a patient who had a long-standing testicular mass had manifested with carcinoid heart disease, which is an uncommon form of carcinoid syndrome. He had manifested with symptoms of right heart-failure, episodic facial flushing and he was found to have severe right-sided valvular heart disease. His urinary 5-hydroxy indole acetic acid level was elevated. He underwent orchidectomy and histopathology of his testicular tumour confirmed a testicular carcinoid tumour.

Zavala-Pompa et al. [5] reported the cases of three patients who had primary carcinoid tumour of the testis. The reported patients were 41 years, 44 years, and 83 years of age. During his initial examination, all three patients had testicular masses with or without associated pain, and none had the carcinoid syndrome. The tumours had measured 4.3 cm, 3.0 cm, and 6.5 cm in dimension. All three tumours had manifested classic histopathology features of carcinoid tumours. The neoplastic cells had exhibited argyrophilia, and all were immunoreactive to chromogranin, serotonin, neuron-specific enolase, and cytokeratin. Two tumours also had positive test results for gastrin and one had positive test results for substance P and vasoactive intestinal polypeptide. None of the tumours had reacted with somatostatin, insulin, pancreatic polypeptide, or placental

alkaline phosphatase. Intracytoplasmic, membrane-bound, round-to-elliptical pleomorphic granules were identified by ultrastructural analysis in all cases. DNA flow cytometric analysis demonstrated a low degree (near-diploid) DNA aneuploidy in all cases, with a DNA index of 1.15 in two tumours and 1.3 in the third tumour. The three patients were alive and well 11 years, 7 years, and 6 months, respectively, after the initial diagnosis of their tumours. A total of 57 cases of this entity, including the 3 reported here, have been reported. Of these, 43 were pure carcinoid, and 14 were associated with teratoma; 6 (11.6%) patients developed metastases. Tumour size and the presence of carcinoid syndrome have been found to correlate with metastatic potential. Neither tumour necrosis nor local tumour invasion (into vessels, tunica albuginea, etc.) correlated with adverse prognosis. Carcinoid tumour of the testis is a rare indolent neoplasm with potential for distant metastases.

Amin et al. [14] reported the cases of three patients who had primary carcinoid tumour of the testis. Amin et al. [14] reported that the patients were 41 years, 44 years, and 83 years of age. During their initial examinations, all three patients were noted to have testicular masses with or without associated pain, and none had carcinoid syndrome. The tumours had measured 4.3 cm, 3.0 cm, and 6.5 cm in dimension. All three tumours had manifested classic histopathology features of carcinoid tumours. The neoplastic cells had exhibited argyrophilia, and all tumours were immunoreactive to chromogranin, serotonin, neuron-specific enolase, and cytokeratin. Two tumours had positive test results for gastrin and one had positive test results for substance P and vasoactive intestinal polypeptide. None of the tumours had reacted with somatostatin, insulin, pancreatic polypeptide, or placental alkaline phosphatase. Intracytoplasmic, membrane-bound, round-to-elliptical pleomorphic granules were demonstrated by the undertaking of ultrastructural analysis in all cases. DNA flow cytometric analysis had demonstrated a low degree (near-diploid) DNA aneuploidy in all cases, with a DNA index of 1.15 in two tumours and 1.3 in the third tumour. The three patients were reported to be alive and well 11 years, 7 years, and 6 months, respectively, after diagnosis. Amin et al. [14] made the ensuing educative iterations:

- A total of 57 cases of this entity, including the 3 cases they had just reported in the article, had been reported.
- Out of these 57 cases, 43 were pure carcinoid tumours, and 14 were carcinoid tumours associated with teratoma; 6 patients that amounted to 11.6% of the patients had developed metastases.
- Tumour size and the presence of carcinoid syndrome had been found to correlate with metastatic potential.
- Neither tumour necrosis nor local tumour invasion (into vessels, tunica albuginea, etc.) had correlated with adverse prognosis.
- Carcinoid tumour of the testis is a rare indolent neoplasm which is associated with the potential for distant metastases development.

Abbosh et al. [6] stated the ensuing:

- Carcinoids are neuroendocrine tumours and most frequently these tumours occur within tissues that are derived from the embryonic gut.
- These tumours could occur within any organ site but are rare within the testis.
- The cell type that gives rise to testicular carcinoid is not known.
- They had postulated that testicular carcinoid might have a germ cell origin.

Abbosh et al. [6] reported their analysis of protein and genetic markers of germ cell neoplasia, utilising immunohistochemistry and fluorescence in situ hybridization, in four testicular carcinoid tumours. Abbosh et al. [6] summarized their results as follows:

- All four cases of testicular carcinoid tumour had arisen in a background of mature teratoma.
- Isochromosome 12p was identified within the carcinoid tumour cells in all four samples.
- 12p overrepresentation was also identified in three cases.
- Isochromosome 12p and 12p overrepresentation were found present in the cells of coexisting mature teratoma in three cases.
- The Carcinoid tumours had exhibited strong immunoreactivity for synaptophysin and chromogranin, but no immunoreactivity for OCT4, CD30, c-kit, TTF-1, and CDX2.
- Membranous and cytoplasmic staining for beta-catenin was detected in three cases.

Abbosh et al. [6] concluded that their findings had indicated that testicular carcinoid tumour represents a phenotypic expression of testicular teratoma and is of germ cell origin.

Lu et al. [9] stated that primary pure carcinoid tumours of the testis (pPCTT) are rare, and there are only a limited number of studies available related to pPCTT. Lu et al. [9] described in their study, the clinicopathological and immune-phenotypical characteristics of 11 cases from their institution between 1978 and 2014, and they reported their experiences of the diagnosis and treatment of these patients. Lu et al. [9] summarized the results as follows:

- The patients ranged in age from 26 years to 68 years old, with a median age of 48 years. One patient (9%) was classified as pT2 and 10 (91%) were pT1.
- Histologically, 7 cases had been diagnosed as classical carcinoid tumours, while the other 4 cases were diagnosed as atypical carcinoid tumours.
- The commonest growth pattern was a mixed insular, acinar, rosetted, solid and trabecular pattern.
- Immunohistochemistry staining studies of the tumour showed the tumour cells had exhibited positive expression of neuron-specific enolase in all cases, and CgA, Syn and CD56 markers in 8 cases that amounted to in 72.7% of the tumours, 10 cases that amounted to 90.9% of the tumours and 9 cases that amounted to 81.7% of the cases, respectively.
- In addition to radical orchidectomy, 9 patients that amounted to 81.7% of the patients received a combined modality of treatment.
- Follow-up data were available for 8 patients.
- Seven patients were alive at the last follow-up without recurrence, and one patient had succumbed to cerebral haemorrhage 7 years pursuant to his surgery.

Lu et al. [9] summated their findings as follows

- Localized pPCTT is a rare disease which is associated an indolent clinical course.
- When a testicular carcinoid tumour is diagnosed, a metastasis or an intestinal primary tumour should be excluded, particularly when the testicular tumour is large.
- A tumour size ≤6.0 cm and the histological appearance had little relation with metastatic behaviour.

Lubana et al. [15] made the ensuing iterations:

- Neuroendocrine tumours were first described by Langhans in 1867. [16]
- The terminology carcinoid (Karzinoide) was coined by a German pathologist Oberndorfer in 1907 and Cope in 1930 had described the first case of metastatic carcinoid tumour which metastasized from small bowel. [17]
- In 1954, Simon et al. had reported the first case of primary testicular carcinoid tumour. [18]
- Primary testicular carcinoid tumours are rare, constituting 0.23% of all testicular tumours.
- Testicular carcinoid tumours (TCT) had been documented to have a mean age at presentation of 46 years and the ages have ranged between 10 years and 83 years [19].
- Even though since 1930 more than 60 cases of testicular carcinoid had been reported, it still remains a very rare diagnosis.

- They were reporting a primary testicular carcinoid tumour of the testis and they were also presenting an extensive literature review to cover all the aspects of carcinoid tumour including the definition, classification, origin, presentation, diagnostic evaluation, management, prognosis, and follow-up.

Lubana et al. [15] reported a 34-year-old man who did not have any past medical history who had manifested with right scrotal swelling for one year, with recent onset of pain. He did not have any history of testicular trauma, haematuria, undescended testis, systemic symptoms, or weight loss. He did not have any family history of testicular cancer. His clinical examination demonstrated an enlarged tender mobile right testicular mass. He had ultrasound scan which revealed an enlarged right testis, heterogeneous in echo texture (5×4.4×4.8 cm) with focal testicular parenchymal hypoechoic mass that measured 1.7 cm ×1 cm × 1.6 cm that was suspicious for neoplastic process (see figure 1).

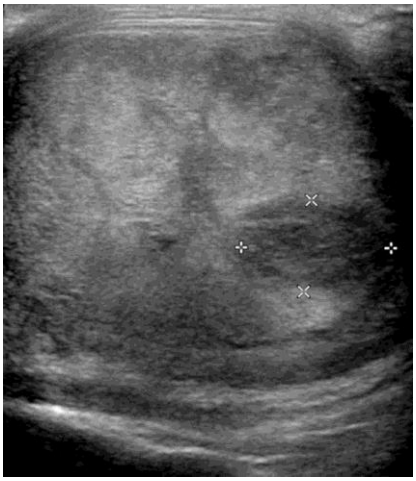

Figure 1: Ultrasound showed enlarged right testis, heterogeneous in echotexture (5.0 x 4.4 x 4.8 cm) with a focal right testicular parenchymal hypoechoic mass-like area (1.7 x 1.0 x 1.6 cm). Reproduced from: [15] Under Creative Commons Attribution License which permits reproduction of figures and contents of the article provided the original source is cited and credited.

Beta human chorionic gonadotropin [β-HCG] and alfa-fetoprotein [AFP] were noted to be normal with elevated lactate dehydrogenase (LDH) 401 (90–225) U/L. He underwent staging computerized tomography (CT) which did not demonstrate any evidence of metastasis or lymph adenopathy. The patient underwent radical orchidectomy. Gross examination of the orchidectomy showed that the right testis and epididymis was covered by intensely fibrotic tunica vaginalis. The testis was found to be entirely occupied by the tumour which measured 4.5 cm × 4.5 cm × 4 cm, with 90% necrosis. The tumour was noted to be confined to the testis and epididymis without lympho-vascular invasion. Microscopy histopathology examination of the tumour demonstrated that the tumour was consistent with a well-differentiated neuroendocrine carcinoma. Histology examination demonstrated nests of monotonous tumour cells with relatively abundant eosinophilic cytoplasm, round to oval nuclei, distinct nuclear membrane with "salt and pepper"-like chromatin (see figure 2). Immunohistochemistry staining studies of the tumour showed that the tumour cells had exhibited positive staining with chromogranin, synaptophysin (see figure 3), cytokeratin AE1/AE3, and CAM5.2 and negative staining for placental alkaline phosphatase, CD30, β-HCG, AFP, and epithelial membrane antigen. Ki-67 labelling index was <1% of tumour cells. The final diagnosis was carcinoid tumour which was localized within the testis. The cancer was classified as pT1 N0 M0 S2 [LDH 401 U/L] as per the American Joint Committee on Cancer (AJCC) TNM staging for testicular cancers.

Figure 2: (A): Low-power view (40x); Showing nests of tumour cells with surrounding abundant blood vessels. (B): High-power view (400x); Monotonous tumour cells with relatively abundant cytoplasm, distinct nuclear membrane with ''salt and pepper''-like chromatin. Reproduced from: [15] Under Creative Commons Attribution License which permits reproduction of figures and contents of the article provided the original source is cited and credited.

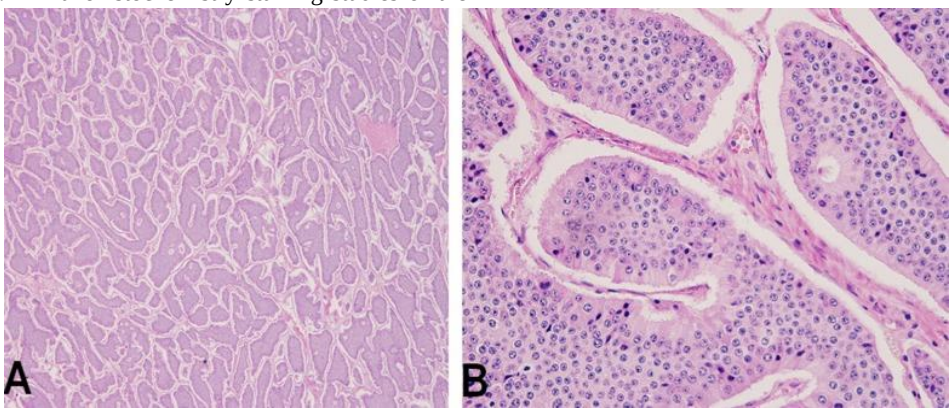

Figure 2: Low-power view (40x); Showing nests of tumour cells with surrounding abundant blood vessels. (B): High-power view (400x); Monotonous tumour cells with relatively abundant cytoplasm, distinct nuclear membrane with ''salt and pepper''-like chromatin. Reproduced from: [15] Under Creative Commons Attribution License which permits reproduction of figures and contents of the article provided the original source is cited credited.

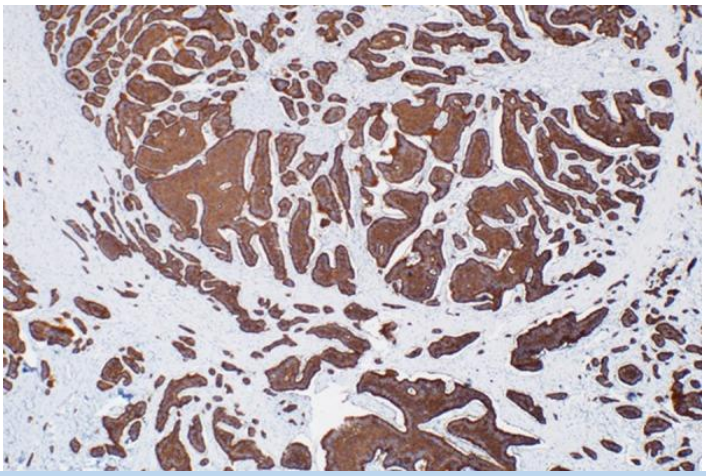

Figure 3: Positive synaptophysin staining of right testis in primary carcinoid tumour. Reproduced from: [15] Under Creative Commons Attribution License which permits reproduction of figures and contents of the article provided the original source is cited and credited.

The possibility of an extra-testicular carcinoid tumour was excluded with negative esophagogastroduodenoscopy and colonoscopy. A nuclear octreotide scan had demonstrated focal radiotracer activity projecting over the scrotum (benign physiologic variant); nevertheless, an octreotide avid tumour could not be excluded. The rest of the body demonstrated no evidence of octreotide avid tumour. Urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) and chromogranin A were within normal range.

Lubana et al. [15] made the ensuing summative iterations:

- Carcinoid tumours are neuroendocrine tumours which do arise from enterochromaffin/Kulchitsky cells.
- These cells are widely distributed throughout the body.
- Nevertheless, carcinoid tumours are not common outside the gastrointestinal tract which tends to be afflicted by 65% of the tumours and the respiratory tract which tends to be afflicted by 25% of the tumours and which are very rarely found within the testis, which could be primary or metastatic [20].
- The neuroendocrine tumours are currently defined or divided into 3 groups by WHO/ European Neuroendocrine Tumour Society (ENETS).
- The classification of the tumour is based upon the immunostaining of Ki-67 or mitotic count – Neuroendocrine Tumours G1 (NET) G1: Ki-67 <2%, NET G2: Ki-67 3–20%, NET G3: Ki-67 >20%.
- The terminology "carcinoid" is utilised for NET G1 [21]
- The histogenesis of pure testicular carcinoma had not been well established.
- It was iterated that testicular carcinoids typically occur within the background of teratoma (a germ cell neoplasm) giving the rationale that testicular carcinoid tumour can be of germ cell origin, which was further supported by immunohistochemistry and Florescence *in situ* hybridization (FISH) techniques used by Abbosh et al. They found that Isochromosome 12p and 12p overrepresentations were present in both the carcinoid tumour cells as well as in the cells of co-existing mature teratoma [6].
- Teratoma could give rise to TCT by various mechanisms.
- Carcinoid tumour of testis might be a component of teratoma with regression of the rest of the elements of the teratoma.
- The other mechanism is the preferential development of Argentaffin cells in teratoma. Nevertheless, Argentaffin cells are not found in the testis but germ cells could give rise to any cell type due to their totipotent capability. [22]
- It has been pointed out that ovarian carcinoid tumour arising as a component [23] or as a malignant transformation. [24] of mature cystic teratoma had been reported. Based upon this analogy similar mechanism is assumed to occur in primary TCT upon literature review. Nevertheless, carcinoid tumour had never been reported to be emanating as a component or resulting from the malignant transformation of teratoma. [25]
- It had been postulated that Leydig cells might be commencing origin of TCT because of their neuroendocrine features. Mai et al. had demonstrated the presence of transitional cells expressing features of both the Leydig cells and carcinoid tumour cells within primary TCT. Also, one out of nine Leydig cell tumours in their study had demonstrated neuroendocrine differentiation. These findings had supported the postulate that both carcinoid tumour cells and Leydig cells might have the same progenitor cell origin in the primary TCT. [25]
- The commonest manifestation of TCT has been documented to be painless testicular enlargement, followed by testicular pain, hydrocele and very rarely cryptorchidism. The duration of symptoms could last as long as 240 months. The left testis had been stated to be the most commonly involved testis with only one report of bilateral involvement of testis. [5] When these tumours are associated with systemic symptoms including episodic wheezing, flushing, and / or diarrhoea, then the terminology carcinoid tumour syndrome is utilised.
- Upon gross macroscopy examination, the tumour does to appear as solid with yellow to tan colour with firm texture due to excessive desmoplasia. The calcifications could be visualised upon gross inspection of the tumour. The average tumour size has been documented to be 4.6 cm and the size of the tumour has ranged from 1.0 cm to 9.5 cm. Microscopy histopathology examination of the tumour does tend to demonstrate that the tumour cells are composed of monotonous polygonal-shaped cells with eosinophilic cytoplasm and finally dispersed chromatin within the uniform bland nuclei. The neoplastic cells could be found to have different architectural arrangements; however, trabecular and insular patterns do tend to predominate. Also, it has been pointed out that necrosis could visualised upon

microscopy histopathology examination of large-sized tumours as well as that mitotic figures are rarely seen. [6] [26]

- It had been advised that the diagnosis of the tumour should entail the ensuing:
    - ❖ Clinicians should commence with clinical examination of scrotum in a patient who manifests with chronic painless swelling of the testis and scrotum.
    - ❖ Doppler ultrasound scan is the initial radiology imaging test of choice.
    - ❖ The diagnosis is established with the help of tumour biomarkers, computed tomography (CT) Scans, Magnetic Resonance Imaging (MRI) Scans, Nuclear medicine techniques like 111 In-Pentetreotide Scintigraphy, 131 MIBG (Meta-Iodobenzylguanidine) and endoscopy.
    - ❖ 5-HIAA is a good initial test for establishing the diagnosis and has a high specificity (100%) but poor sensitivity (<35%).
    - ❖ Plasma Chromogranin A (CgA) is the most accurate tumour biomarker among all the available markers. CgA has higher sensitivity (68%) but lower specificity (86%) for the detection of carcinoid tumours than 5-HIAA. The CgA is useful in ascertaining if the tumour is local or metastatic, syndromic or non-syndromic. Its level does correlate very well with the extent of the tumour burden, the higher the levels, the worse the prognosis. The usefulness of CgA extends to assess the response to therapy. It has high accuracy in comparison with urinary 5-HIAA for the detection or identification of relapse in carcinoid tumours. [27]
- It has been documented that patients who are diagnosed as having TCT very rarely could express features of carcinoid syndrome but only if there is metastasis to the liver or lungs. [28] Therefore any patient manifesting with symptoms of serotonin excess and testicular swelling should undergo a 24hr urinary 5-HIAA test prior to undergoing surgery. [29] It has been pointed out that because it is difficult to suspect testicular carcinoid pre-operatively and 5 HIAA taken prior to surgery would serve as the baseline tumour marker if the tumour turns out to be carcinoid. [30] Platelet serotonin is the sensitive marker for detection of carcinoid tumour especially if the carcinoid tumours have low serotonin production. This makes platelet serotonin estimation a reliable tool for the early diagnosis of the carcinoid tumour and also an excellent marker for the detection of residual tumour following surgery. [31]
- It is important to meticulously investigate for a primary tumour since 10% of the TCTs do have extra-testicular primary tumour. The diagnosis of primary TCT is made only after the exclusion of extra-testicular primary tumour since the morphology and histopathology examination features of the primary and metastatic TCT is same. [5]
- Staging CT scan is utilised for the detection of metastasis.
- 111 In-Pentetreotide scintigraphy has a sensitivity of 80–90% to localize the tumour and could also be utilised to predict the response to octreotide therapy. 131-MIBG has a lower sensitivity in comparison with scintigraphy scan. Sensitivity in detecting the tumour could be increased to 95% by combining both the scans. When bone metastases are suspected bone scintigraphy should be undertaken since it has a higher sensitivity (90–100%) than 111 In-Pentetreotide scintigraphy (sensitivity-50%) and 131 I-MIBG scan (sensitivity-20%). Video capsule endoscopy is a more advanced technique for the identification of primary carcinoid tumour in the small bowel and thus early resection. [20] It is stated to be a reasonable small bowel imaging technique since carcinoid tumours are mostly found in ileum [19].
- Radical orchidectomy is the treatment of choice.
- Carcinoid tumours generally tend to have a very poor response to chemotherapy or radiotherapy. Symptomatic treatment should be provided to the patients who have carcinoid syndrome. Octreotide, a somatostatin analogue does inhibit the release of hormones and neurotransmitters and thus causing symptomatic improvement in about 80% of the patients [20]. The slow-release preparations of somatostatin analogues are available (Sandostatin LAR(R) Depot).
- The octreotide has variable antiproliferative effect ranging from partial to complete regression of metastatic carcinoid tumour. Leong and Pasieka had reported 2 cases of metastatic carcinoid tumours in which octreotide was administered for symptomatic treatment before the debulking surgery. The reported previously seen radiographic metastatic lesions were found to have regressed completely during laparotomy. [32]
- Because of improved prognosis and longer survival time as a result of advanced diagnostic and therapeutic techniques other late complications involving metastasis to skin and skeletal system and carcinoid heart disease (CHD) had been reported. [33] [34] Long term follow up is recommended due to the fact that delayed metastasis had been reported even up to several years with one case of metastasis occurring after 17 years pursuant to his initial diagnosis [22]. Multimodal approach could be tried where tumour recurrence is highly suspected. Considering that there are no standardized protocols for the follow up assessment of patients who have undergone treatment for carcinoid tumours of testis, annual physical examination and frequent Urinary 5HIAA would be a reasonable approach. CgA is of particular importance when the 5 HIAA comes out to be normal in a patient after the undertaking of orchidectomy, since normal 5 HIAA does not exclude the presence of tumour recurrence or metastasis [19]. Sutherland et al. recommended 3 monthly follow up with 5 HIAA measurement for the first year and then annually [29]. Utilization of platelet serotonin is valuable in the detection of residual tumour following surgical resection of the tumour [31]. If still there is any doubt of tumour recurrence or metastasis, 111 In-Pentetreotide scintigraphy can be used [19].
- The carcinoid tumours in general do portend an excellent prognosis due to their indolent course. Aggressiveness of the carcinoid tumours is stated to be directly proportional to the size of the tumour (>7.3 cm) and evidence of carcinoid syndrome [29]. The prognosis of carcinoid tumour was stated to depend upon the extent of tumour spread. 5-year survival rate for localized disease was stated to be 93% and for distant metastatic disease was stated to be between 20% and 30% [20]. Only 3 deaths had been reported related to distant metastasis [5]. Since there is no effective treatment available for metastatic lesion(s) the prognosis has tended to be poor. So far there had been only one case report where the metastatic lesion was removed by surgical excision. No new metastases were documented to have been found after 25months of follow up assessments [35] .

Lubana et al. [15] made the ensuing educative concluding iterations:

- Their reported case had added to the rare reports in the literature of a primary carcinoid tumour of the testis having low malignant potential.

- Because of the advanced diagnostic and treatment modalities, the survival time had prolonged but long-term complications like CHD and bone and skin metastasis had emerged.
- Serotonin levels could be elevated even in the absence of carcinoid syndrome.
- The elevated levels of serotonin could cause CHD leading to reduced survival and poor quality of life; hence, it is important to follow the hormone levels. High-risk cases that have tumour size greater than (>) 7.3 cm, presence of carcinoid syndrome, poorly differentiated tumours and tumours associated with invasion, should be followed more closely for follow-up assessments for the development of recurrence and development of metastasis.
- This follow-up assessments should be undertaken by monitoring biochemical markers on a regular basis and in case of doubt, scintigraphy / radiology imaging should be undertaken. The surgery should be undertaken if the metastatic lesion(s) is/are resectable and if not accessible for resection, a trial of octreotide therapy could be given because of its antiproliferative and antihormonal properties. It is important to exclude metastasis in case of testicular carcinoid tumour because the morphology and histology features of the tumour cannot distinguish between the primary tumour and metastatic tumour.

Amine et al. [36] studied the main epidemiological, clinical, para clinical, pathological, therapeutic, and evolutionary features of patients who had testicular neuroendocrine tumours (TNET). Amine et al. [36] identified nine case series and sixteen case reports by searching PubMed database and qualified for inclusion in this study. Amine et al. [36] added the data of one case treated in the department of urology in Habib Bourguiba Hospital in Sfax, to the published cases. Amine et al. [36] summarized the results as follows:

- A total of 132 cases were collected.
- The median age of the patients at the time of initial diagnosis was 39 years old with an age range between 10 years and 83 years.
- The most common manifesting symptom was either a testicular mass or a swelling in 38.46% of cases.
- Carcinoid syndrome was recorded in 10.60% of patients.
- The physical examination had demonstrated a palpable mass in 44.70% of the patients.
- The mass was painless and firm in majority of cases.
- Serum tumour markers (serum Beta Human chorionic gonadotrophin, alpha feto protein, and lactate dehydrogenase, levels were within normal limits in all patients except in one case.
- Majority of the testicular neuroendocrine tumours that amounted to 76.52% of the tumours were primary and pure.
- The tumours were positive for chromogranin in 100% of the tumours, synaptophysin in 100% of the tumours and cytokeratin in 93.10% of the tumours.
- Metastases were identified at the time of initial diagnosis in eight cases that amounted to in 6.06% of the tumours.
- The main treatment was radical orchiectomy which was undertaken in 127 patients that amounted to in 96.21% of the patients.
- The 5-year overall survival rate of the patients was 78.70% and the 5-year specific survival rate was 84.30%.

Amine et al. [36] made the ensuing conclusions:

- The diagnosis of testicular carcinoids is based upon the immunohistochemistry study.
- The treatment of choice for these tumours is radical orchidectomy.
- Somatostatin analogues were reported to be effective in patients who had carcinoid syndrome.

Reyes et al. [8] studied 10 cases of primary pure testicular neuroendocrine carcinoma. Reyes et al. [8] reported that the patients were between 16 years and 48 years old and they had testicular swelling with pain or a painless testicular mass and no history of neuroendocrine carcinoma or other malignant neoplasm. All 10 patients underwent orchidectomy. The tumours were low (n = 9) and intermediate (n = 1) grades with a variegated histopathology appearance that was characterized by a nesting pattern, cords of neoplastic cells with rosettes, or sheets of neoplastic cells. Mitotic activity was noted to be lacking in 9 cases. In 1 case, mitotic-figures were noted to have ranged from 7 to 8 per 10 high-power fields, and cellular atypia and comedo-like necrosis were observed. Immunohistochemistry staining studies utilising a keratin cocktail, chromogranin, synaptophysin, epidermal growth factor, p53, placental-like alkaline phosphatase, and CD117 (c-kit) were undertaken in all cases. Keratin, chromogranin, and synaptophysin were positive in all tumours. Clinical follow-up information was obtained for 6 patients and the follow-up had ranged between 12 months and 60 months; 5 of the patients who had low-grade tumours were alive 24 to 60 months after the initial diagnosis; 1 patient who had an intermediate-grade tumour died of his tumour 12 months after the initial diagnosis. Han et al. [8] stated the following:

- The behaviour of these tumours, while in the testicular region, correlated well with the histological grade.
- They proposed replacing the terminology testicular carcinoid with neuroendocrine carcinoma, which better reflects the nature of these tumours. .

Han et al. [37] explored the clinicopathological characteristics and differential diagnosis of primary neuroendocrine tumour (G1) of the testis. Han et al. [37] analysed the clinical, histomorphology and immunohistochemistry staining study findings, treatment and prognosis of a patient who had primary neuroendocrine tumour of the testis, and discussed the relevant literature. Han et al. [36] reported a-52-year-old man who had manifested with a painless testicular swelling over a period of 6 months. Histopathology examination of the testicular tumour mass demonstrated that the tumour cells were arranged in island and beam patterns. The tumour cells were noted to be uniform, polygonal and had moderately eosinophilic cytoplasm and fine granular nuclear chromatin. Immunohistochemistry staining studies of tumour demonstrated that the tumour cells had exhibited positive staining for cytokeratin, CD56, synaptophysin and chromogranin A, and negative for inhibin, placental alkaline phosphatase and alpha-fetoprotein. Han et al. [37] stated the following:

- Primary neuroendocrine tumour of the testis is a rare tumour which has characteristic radiology imaging features.
- Its accurate diagnosis depends upon the morphology and immunohistochemistry staining study features.
- These tumours need to be differentiated from metastatic neuroendocrine carcinomas, teratomas with carcinoid, seminomas, Sertoli cell tumours and granulosa cell tumours.
- The treatment of most primary neuroendocrine tumours entails surgical resection combined with other treatments and usually results in a good prognosis.

Albalawi et al. [48] stated that testicular neuroendocrine tumours (TNETs) are extremely uncommon. rare. Albalawi et al. [48] reported a 47-year-old man who manifested with a painless right testicular mass. The results of all his tumour markers levels were within normal ranges. The patient underwent a high inguinal radical orchidectomy. Histopathology examination of the orchidectomy specimen demonstrated a well-differentiated neuroendocrine tumour. He underwent radiology imaging investigations which demonstrated multiple prominent axillary, supraclavicular, mediastinal, and hilar lymph nodes and no bowel or mesenteric lesions suggesting carcinoid. Albalawi et al. [] stated the following:

- Once a TNET is diagnosed, it is necessary to exclude secondary origin in the gastrointestinal tract and lungs.
- Radical orchiectomy is the treatment of choice for TNETs.
- Somatostatin analogs could be useful in patients who have carcinoid syndrome, i Somatostatin analogs could induce symptomatic improvement, and they could control progression of the tumour.
- As their reported case had highlighted, it is important for physicians to consider TNETs in the differential diagnosis of testicular masses, as early diagnosis and treatment are crucial for good patient outcomes.

Conclusions and Summary

- Neuroendocrine tumours (NETs) constitute a group of malignancies that arise from neuroendocrine cells throughout the body, usually they had been called carcinoid tumours.
- Most of NETs could manifest within the gastrointestinal tract
- Other sites for the manifestation of NETS include the lung, biliary tract, pancreas, ovaries, thymus, and rarely, the testes.
- Neuroendocrine tumours of the testis account for than 1% of all testicular tumours
- TNETs are extremely uncommon but overall TNETs do have a good prognosis.
- Once a TNET is diagnosed, it is important for all clinicians to exclude secondary origin of the tumour within the gastrointestinal tract and lungs.
- The treatment of choice is radical inguinal orchiectomy with close follow-up, while the indications for the undertaking of retroperitoneal lymph node dissection in pure primary TNET has not been clarified yet.
- Adjuvant treatments for TNETs include chemotherapy, radiotherapy, somatostatin analogs, and α-interferon.
- Clinicians need to should include TNETs in the differential diagnosis of testicular masses, due to the fact that early diagnosis and treatment of TNETs are crucial for good patient outcomes.

Conflict of Interest – nil

Acknowledgements

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DOI:10.31579/2640-1045/164