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Sarcoidosis of The Testis

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Abstract

Sarcoidosis of the testis is an extra – pulmonary manifestation of sarcoidosis. The testes may be involved in isolation or with other reproductive organs like the epididymis, and vas deferens. It could also occur as part of a multi – systemic disease. A varied presentation is possible, with possible impact on fertility. Various search engines were used to retrieve reports on testicular sarcoidosis (TS). Information was analysed with SPSS version 20. Salient features of TS obtained from the review include: TS is not as uncommon as we may think. TS has been reported as frequently as sarcoidosis of the epididymis, co-existing with the latter in 26.5% of cases. TS is most common in blacks and presents most often as a painless scrotal swelling. Corticosteroids are the approved and most efficient form of therapy.

Keywords: Sarcoidosis of the testis, Kveim test, Kveim – Sitzbach test, medical therapy, surgical therapy, watchful waiting.

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Introduction

Sarcoidosis was first described as a cutaneous manifestation in the 19th century by Jonathan Hutchinson who referred to it as 'Mortimer's malady' and then by Ernest Bessnier who called it 'lupus pernio'. Caesar Boeck studied it in more detail and reviewed it histologically, describing the lesions as 'compact sharply defined tumour foci' which had some giant cells which were abundant epitheloid cells with large pale nuclei. [1] He coined the term 'sarkoid' to refer to the skin nodules which resembled a benign sarcoma. [2, 3] In 1916 he acknowledged it as a 'general' disease able to affect multiple organs.

The diversity of the disease has led to it having no strict definition, but rather only a description. The American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) [3] described it in 1999 as: "a multi-systemic disorder of unknown cause" which "commonly affects young and middle-aged adults"….. "The diagnosis is established when clinico-radiographic findings are supported by histological evidence of non - caseating epitheloid cell granulomas. Granulomas of unknown causes and local sarcoid reactions must be excluded."…… "The course and prognosis may correlate with the mode of the onset, and the extent of the disease. An acute onset with erythema nodosum or asymptomatic bilateral hilar adenopathy usually heralds a self-limiting course, whereas an insidious onset, especially with multiple extra–pulmonary lesions, may be followed by relentless, progressive fibrosis of the lungs and other organs." [3]

The non–cutaneous manifestations of sarcoidosis and its ability to affect internal organs was further established and demonstrated by Schaumann, Kuznitsky and Bittorf. [1]Since then, it has been described in multiple internal organs other than the lungs.

The first report of testicular sarcoidosis is attributed to Nickerson [4] in 1937. Contrary to many authors' depiction of this being by Schaumann in 1936, Schaumann actually documented testicular atrophy in the post mortem findings of the classic four patients he reviewed. The histology of the testes in the report showed no evidence of sarcoidosis but on rather, sarcoid granulomata in both epididymides. [5]

Literature review

General overview

Epidemiology

Sarcoidosis, in its classical form, shows a consistent predilection for adults less than 40 years of age. [3]It affects 1 – 6/1,00,000 persons worldwide.[6] It has an increased life time risk, severity and incidence of extra – pulmonary manifestations in blacks. [3,7,8] Genitourinary involvement occurs in 0.2% of cases, and affects African Americans 10 – 20 times more than their Caucasian counterparts [9,10]. The age of predilection for genitourinary sarcoidosis was reported as 33 years of age with 58% being African American. [11] Porter [12] reported it to be 31 years of age. Only 2% of all African Americans who presented with sarcoidosis at health centers within Atlanta, United States of America had sarcoidosis affecting the reproductive organs. [7] (This value was not restricted to testicular involvement alone, but includes all male and female reproductive organs).

Sarcoidosis of the testis (SOT) is rare [13] and predominantly affects blacks between the ages of 20 and 40 years. [14]Very few cases have been reported among children. In a review of 33 children, only one had SOT. [15]SOT is four times as common in blacks as whites [11] and affects 47 - 58% of patients with genital sarcoidosis [11,16]. The testes are documented to be the second most common genital organs affected by sarcoidosis, after the epididymis. [11] The vas deferens and prostate come next, in that order. [11] It has been documented that a third of cases have bilateral involvement. [17] Another review stated that 10% of cases of TS have bilateral testicular involvement. [4] As if by way of contradicting the initial differential prevalence, McWilliams [18] stated that almost all cases of ST co-exist either epididymal involvement.

A low level of suspicion for sarcoidosis and high level of suspicion for testicular malignancies has led to "aggressive" [19] treatment in the form of orchidectomy or wedge biopsies. These procedures may also include retroperitoneal lymph node dissection. [11]

The discussion in this literature review would be restricted to sarcoidosis of the testis and would exclude extra–testicular sarcoidosis associated with testicular malignancy. [13, 20] As a rule of thumb in the diagnosis of rare manifestations of sarcoidosis, a diagnosis is made in the presence of a compatible clinical presentation, non–caseating granulomas on histology and the exclusion of other possible causes. [8, 13]

Aetiology

The aetiology of sarcoidosis is largely unknown. [2, 3, 14] The ACCESS (A Case–Control Etiologic Study of Sarcoidosis) study showed that no single aetiologic agent was responsible for sarcoidosis in isolation but various aetiologies worked together to increase the risk for and potential to develop the disease. [21] It could develop as a result of a testicular malignancy. There have been case reports of testicular sarcoidosis after the detection and treatment of primary testicular cancers. [14] Immunologic polygenic inheritance of HLA A, B8 and DR3 have been implicated in an excessive triggering of the cellular immune response to immunogens. [3] Occupations associated positively with sarcoidosis include those who work in mobile homes, gardens, or work with insecticides, wood, copper or textiles or generate biological aerosols. [21, 22] Examples of these general and specific aetiologies are depicted in Table 1 below:

General aetiology	Specific aetiologies	Examples
Infections	Mycobacteria Fungi Viruses Bacteria Spirochaetes Parasites	Mycobacterium tuberculosis, M. leprae Histoplasma spp, Coccidioides spp EBV, HIV, Rubella, Measles Brucella spp, Borrelia spp Treponema pallidum Schistosoma spp
Neoplasms	Carcinoma	Malignancy associated granulomas
Metals		Copper, [23] Beryllium, Aluminium [3]
Immune disorders		Grave's disease, [24] psoriasis, [14] Common variable immune deficiency
Vasculitides		Takayasu vasculitis, [25] Wegener's granulomatosis
Miscellaneous	Recreational drugs	Cocaine [24]

Table 1: Potential aetiologies for sarcoidosis (Not proved by results obtained from ACCESS). Adapted from "Aetiologies of sarcoidosis" by L S Newman [22]

The Pathology of Testicular Sarcoidosis

Macroscopically, the testis may look enlarged, brown or tan, and be encased in white fibrous tissue [26] on the contrary, the testis may be atrophic and fibrotic. [26] Tenneson was the first to give a description of the histological appearance of sarcoidosis in 1892. [2] This was elaborated upon by

Boeck. [2] Scadding and Mitchell defined sarcoidosis, based on the histological appearance of the lesions, as a "disease characterised by the formation in all of several affected tissues of epithelioid-cell tubercles without caseation though fibrinoid necrosis may be present at the centre of a few, proceeding either to resolution or to conversion into hyaline fibrous tissue". [2]

The granulomata have multinucleated giant cells that commonly have cytoplasmic inclusions like asteroid bodies, Schaumann bodies or crystalline particles which are usually colourless, anisotropic, refractile and made of calcium oxalate. [27, 28] Less often, the granulomata are of the Langhans variety. [29] Asteroid bodies (also known as radial inclusion bodies) are stellate inclusions located in vacuoles with numerous rays radiating outward in a centripetal manner. [30] The crystalline bodies may be the nidi initiating the formation of Schaumann bodies. These are named after Schaumman who first described sarcoidosis involving the testis, and are conchoidal bodies comprising calcified layers of calcium crystals. [28] They stain deeply with haematoxylin or stains for iron or calcium, because they contain these metals. These are depicted in Figure 1. They are usually extracellular. [29] They are not exclusive to sarcoidosis and may be seen in berryliosis, another chronic granulomatous disease. [30]

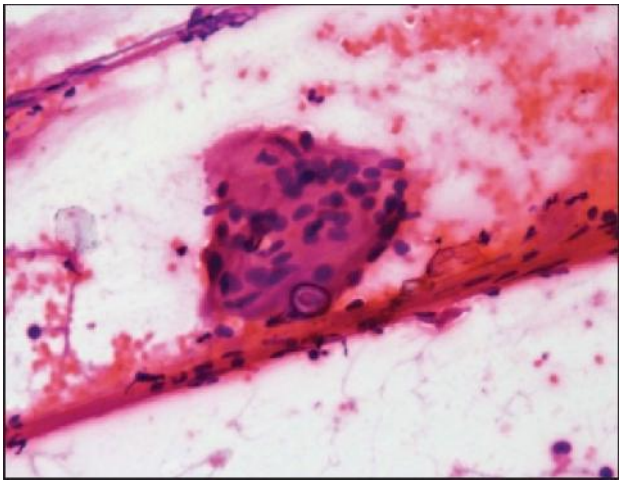

Figure 1: A Schaumann body is shown within a multinucleated giant cell (From Gupta N, Rajwanshi A, Gupta D. Schaumann body in a case of sarcoidosis diagnosed on transbronchial FNAC. With the kind permission of *J Cytol*. 2011;28(2):88-89. All rights reserved. Articles published by this open-access journal are distributed under the Creative Commons Attribution Non-Commercial Licence-Share Alike 3.0 Unported, which permits use, distribution, and reproduction in any medium provided the original work is properly cited, the use is non-commercial and is otherwise in compliance with the licence)

Although there may be eosinophilia, eosinophils are infrequent in granulomata. Lymphocytes are more numerous. Plasma cells are seldom seen. On rare occasions, neutrophils are present in the granulomata. [30] There may be hyalinisation of the seminiferous tubules, which may be seen as thickening and tubularisation of the basement membranes. Complete atrophy of the seminiferous tubules and substitution for hyalinised masses has been reported. [26] The spermatogonia may be dystrophic or absent.

The granulomata have increased α-hydroxylase activity leading to increased vitamin and calcium metabolism, with resultant elevations in urine and serum calcium levels. The parathyroid hormone levels of such patients may be normal or low.

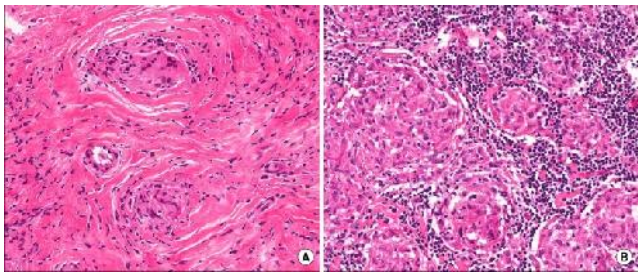

Figure 2: Non–caseating granulomata in A: testicular sarcoidosis; B: an inguinal lymph node biopsy of same patient (From Kim YB, Chung YG, Kim SJ, et al. Extensive systemic sarcoidosis with testicular involvement mimicking metastatic testicular cancer. Korean J Urol. 2011;52(4):295-297 - an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited).

The granulomata become surrounded by fibroblasts, hyalinise. A scar then replaces the granulomata. [29] Clinically and radiologically, this is recognised as spontaneous resolution of the lesions. [29, 30]

Various stains could be used to rule out other pathologies. These include Grocot-Gomori's methenamine silver, Kinyoun's acid-fast stain, and Warthin-Starry stain to exclude fungi like Pneumocystis jiroveci, acid-fast bacilli (AFB) such as Mycobacteria, and spirochetes, respectively. [31]

Caseating granulomatous sarcoidosis lesions, with or without granulomatous vasculitis, have been reported, however, these are uncommon. [32, 33] They are also difficult to differentiate from other causes of caseating granulomas like tuberculosis (TB), fungal or spirochete infections. This can be done using the specific stains elaborated upon previously. This variant was first described by Ricker and Clark in 1949 and named Necrotising sarcoidosis granuloma (NSG) by A.A. Leibow in 1973. It has been found to affect those between the fourth and sixth decades predominantly [32], with eye and the central nervous system being the most affected. [32,34] NSG has been described as an intermediate entity between sarcoidosis and a computerize vasculitides. [32] Another school of thought however believes it to be distinct from sarcoidosis.

[35]Controversy over the nomenclature also exists. "Nodular sclerosis" has been used for similar lesions with bilateral pulmonary nodular involvement mimicking metastatic lesions. [34] Rosen believes these to be one and the same, and suggests a review of the nomenclature to "Sarcoidosis with NSG pattern". Literature maintains this entity has a good prognosis and responds well to corticosteroid therapy, excision or observation. [32–35] We found only one case of caseating granuloma in a patient with SOT. [33]

Clinical features

It may be asymptomatic and be discovered posthumously [25] or as an incidental radiological finding. [36] SOT may present in an isolated manner or in conjunction with other genitourinary involvement as a diffuse, painless, nodular unilateral testicular mass. It could also present with bilateral involvement that could occur either synchronously or sequentially. [37] It has been known to sometimes affect the epididymis concurrently. [14] It could present less commonly as acute epididymorchitis. [10]

Porter [12] has described that SOT could manifest as primary testicular failure with low testosterone levels, oligospermia and infertility. Leydig cell dysfunction could affect the attainment of secondary sexual characteristics. [12]

Constitutional symptoms like fever, night sweats, weight loss with or without lymphadenopathy may be present. The patient may manifest features of hypercalcaemia like nausea, vomiting, and/or abdominal pains. [38] The patient may also show symptoms and signs of involvement of other organs by the disease process.

Differential diagnoses

TB affecting the testis is a strong differential diagnosis of SOT. [13] The patient may or may not present with a history of cough or contact with person with a chronic cough. There may be night sweats and weight loss. The histology would show caseating granulomata. [39] Unfortunately, further compounding issues of differentiating one from the other, is the fact that TB could co-exist with sarcoidosis. [5,38]

A testicular tumour is another differential diagnosis. There is a tendency to manage testicular masses as malignant ab initio, till malignancy is excluded. [14] The presence of abdominal, retroperitoneal or intrathoracic lymphadenopathy, and/or the presence of pulmonary lesions can increase the suspicion of a metastatic testicular malignancy,

It is sometimes difficult to distinguish between an immunologic response to a testicular tumour, resulting in sarcoid lesions discovered following treatment for a testicular malignancy and actual SOT. [40]

Granulomatous lesions of unknown significance (GLUS) syndrome can be distinguished from SOT as the non-caseating granulomata are B cell-positive, as opposed to those of sarcoidosis which are B cell-negative. [3] Granulomatous orchitis is another differential of SOT. [41]

Behcet's disease [42] and cholesterol granuloma(ta) [43] of the testis may present with testicular masses as well. Other differentials include syphilis, sperm granuloma, filarial granuloma, lymphogranuloma venereum, granuloma inguinale, blastomycosis, coccidioidomycosis, actinomycosis, schistosomiasis, and Wegener's granulomatosis. [44]

Investigations

The choice of investigations should be aimed at establishing a diagnosis, the extent of complications, stability of the disease and determining if the patient is likely to benefit from therapy. [3]

Radiological investigations: A scrotal ultrasound scan will detect a hypoechoic, but sometimes, hyperechoic nodule [45] in the testis. It will also detect concomitant epididymal involvement where present. [14] McWilliams [18] stated that almost all cases of testicular sarcoidosis co–exist with epididymal sarcoidosis. Lesions are usually multifocal and not solitary. [46] A solitary lesion increases the suspicion of malignancy. [46] Hydroceles may be noted on the ultrasound scan. [19] These may be secondary to sarcoidosis. [47]

A chest X-ray may show various degrees of pulmonary involvement which can be graded according to the description by Scadding, from 0 – IV. [48] There may also be pleural effusion. [49] Bilateral hilar and para-tracheal-nodal-enlargements may be seen and this is termed the "Garland" or "1 – 2 – 3" sign. [50]

Findings from computerized tomographic scans (CTS) of the chest may mimick findings of the chest X-ray and may give additional information of mediastinal, para-tracheal, aortocaval window, peri-clavicular or other lymphadenopathy. [24] It may also the "tree – in – bud" or "bud fashion" appearance that signifies centrilobular nodules. [51] An abdominal or pelvic CTS may show retroperitoneal, peri-iliac or other forms of regional lymphadenopathy. [24] The presence of retroperitoneal lymphadenopathy increases the suspicion of a malignant lesion and the chance of having an orchidectomy offered as a therapeutic option. [52]

Better resolution may be obtained with a T2 weighted MRI which would show a hypo-intense

contrast-enhancing testicular lesion. [14] Some recommend it as a better option than CT in the investigation of SOT. [38]

A "Panda" or "Lambda" pattern on a Gallium-67 body scan suggests sarcoidosis. The former refers to increased radioactive uptake by lacrimal and salivary glands as well as the nasal area, while the latter describes increased uptake by para-tracheal and hilar nodes. [53] A gallium scintigraphy may be indicated in patients with negative chest X-ray findings and little or no demonstrable pulmonary involvement or negative biopsies. [3, 53]Hot spots in the testis could also be seen on gallium scintigraphy.[54]

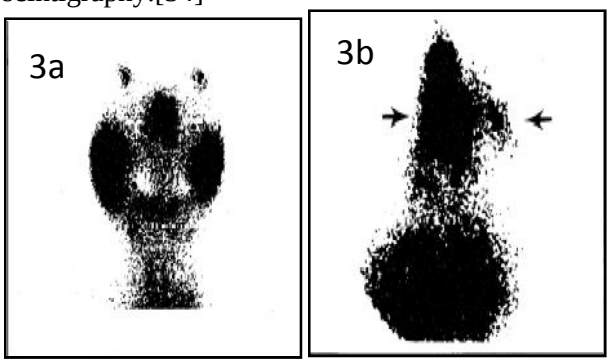

Figure 3a: Panda sign; Figure 3b: Lambda sign (From Caglar M, Naldoken S. "Panda" and "Lambda" Signs in Sarcoidosis: Patterns to Recognize on Gallium Scintigraphy. TJNM 1992; 1: 50-51. This is an open access article distributed under the Creative Commons Act Creative Commons Attribution Non-Commercial License [No Derivatives 4.0 International: CC BY-NC-ND 4.0] which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited)

It has been reported that up to 84 % of patients with sarcoidosis have pulmonary involvement, [55] so a bronchoalveolar lavage (BAL) could be done for patients with suspected TS. The findings are suggestive of sarcoidosis if there is a reversal of the CD4:CD8 ratio, and levels of activated T cells, immunoglobulins and/or IgG – producing cells are elevated. [37, 56] A 100% positive predictive value for sarcoidosis was associated with the "triad of a CD4 to CD8 ratio greater than four to one, a lymphocyte percentage greater than or equal to 16 percent, and a trans-bronchial biopsy demonstrating non–caseating granulomas" [57] other investigations possible include an endoscopic ultrasound scan, fibre-optic bronchoscopy, and mediastinoscopy, each, with a biopsy if a lesion is found. [56]

Histological investigations: Svetec [55] recommends taking biopsies form accessible sites for example, enlarged lymph nodes instead of invading the sanctity of the scrotum. Many other authors biopsy the testicular nodules, either as frozen sections [58] or partial excisions/ nodulectomies. [59]Fine needle aspiration cytology (FNAC) of superficial lesion like lymph nodes[10] and submental masses [19] have been used to make a diagnosis of SOT.

Biochemical tests: Foetal tumour markers such as α-fetoprotein (AFP), β–human chorionic gonadotrophin (β-HCG) and lactate dehydrogenase (LDH) would be negative in SOT as opposed to testicular malignancies. [14]A case report of elevated testicular tumour markers in a Caucasian with testicular sarcoidosis however, exists [16] and it has been noted that AFP can be raised if there is hepatic involvement by sarcoidosis. [24]As a general, though debatable, [9] rule of thumb, testicular cancer affects Caucasians more while testicular sarcoidosis is seen more in African Americans between the ages of 20 and 40 years, so a Caucasian with a testicular mass within this age bracket should be more thoroughly evaluated for a malignant testicular tumour than his black male counterpart. [14, 60] LDH levels may also be raised in lymphoma. A presentation of SOT with bilateral testicular involvement would increase the suspicion of lymphoma. [61]In some case reports, LDH was elevated when the patient had pulmonary sarcoidosis, before testicular manifestations began, which shows how non – specific the use of LDH is for SOT. [24, 62]

Non–specific biochemical markers may also be elevated such as Angiotensin converting enzyme (ACE) and/or Interleukin 2. [14]A high index of suspicion may occur if ACE levels exceed 200% of the normal values, but then again, this may also occur in tuberculosis, combined variable immunodeficiency or Gaucher's disease. [3, 56]ACE levels may be elevated due to concomitant pulmonary or hepatic involvement [56], further implying that it may not be elevated in SOT if these organs are not affected. ACE levels are elevated in less than 10% of granulomatous diseases [63] as opposed to other serum markers like serum lysozyme, [64] which may also be elevated in sarcoidosis. Normal ACE levels have been documented as well in confirmed cases of testicular sarcoidosis. [37]C–reactive protein, an acute phase reactant may also be elevated. [65]Angiotensin II may be elevated where there is co-existing pulmonary involvement. [66]

Serum calcium and urinary calcium levels may be elevated in those with increased α-hydroxylase activity within the granulomata. A-hydroxylase is necessary for vitamin D formation. Increased vitamin D formation results in increased intestinal absorption of calcium not responsive to normal physiologic feedback mechanisms. There are also increased bone resorptive tendencies from the excess circulating vitamin D, to further exacerbate hypercalcaemia and/or hypercalciuria. [14,67] A normal level of serum calcium does not rule out sarcoidosis. [37]

Haematological test

A complete blood count of patients with SOT may show eosinophilia. [19] Mayock et al [68] reported that 25% of the 145 patients reviewed with sarcoidosis of different organs had eosinophilia.

The erythrocyte sedimentation rate (ESR) may be elevated in SOT as well. [69]

Immunological tests: The 'Nickerson–Kveim', 'Kveim' or 'Kveim–Sitzbach' test involves injecting suspensions of sarcoid tissue subdermally and taking biopsies in about four weeks from the site. It is positive if it yields a sarcoid granuloma. [70] It yields true positives in >50 % of cases and gives false positives almost 0% of the time. [71]

A purified protein derivative of tuberculin could be injected subdermally. There is usually anergy to it in patients with sarcoidosis; however, there may be positive tuberculin tests in those with a high tuberculin sensitivity. [30]

Endocrine tests: A hormone profile may be indicated as reports of hypogonadism with low serum testosterone and even, diminished hypothalamic function have been reported in patients with sarcoidosis of the testis [26, 72]. It is recommended that semen analysis should be done for every man with the intention of fathering a child, once sarcoidosis is diagnosed. [55] Azoospermia, [23] oligospermia of various degrees, [58] or even oligoasthenoteratozoospermia (OAT) [73] have been recorded in patients with testicular sarcoidosis, with or without epididymal involvement.

Miscellaneous test: A *P*ulmonary function test may be essential to determine the extent of restrictive lung disease. [56]

Treatment: It is important to individualize treatment options, duration and follow–up. [74] Treatment may be classified into watchful waiting, medical or surgical therapy. Multiple permutations and combinations of care have been used.

Watchful waiting

Demographics may guide therapy. For example, a young black man has a low risk of having a testicular malignancy, and a higher risk of sarcoidosis than a white man. [19]Thus, the black man may be treated ab initio as a case of sarcoidosis. This is controversial. Porter [12] reported an incidence of testicular cancer among blacks to be as low as 1.2–3.5% but Rohani [24] raised the need for caution when he highlighted the fact that the age grade for sarcoidosis is the same as that for testicular malignancies.

Lesions could regress spontaneously within a two year period, [14] but could also proceed to extensive fibrosis in about 20% of cases. [3] It has been documented that 50 – 70% of lesions resolve without any therapy, therefore some authors do not recommend any treatment. [75]

Indications for watchful waiting may therefore be:

- Young black man [19]
- Bilateral lesion [76]
- Negative testicular tumour markers [76]
- Negative investigations for tuberculosis
- No other system involved by sarcoidosis [77]

Medical therapy

In 1951, H.Isreal suggested the use of corticosteroids in the treatment of sarcoidosis. [2] High dose corticosteroids are required, to reduce the oedema. The sarcoid lesions persist for weeks to months thereafter. [13] There may be complete regression with corticosteroid therapy [54] or persistence despite corticosteroids. The duration of therapy instituted is determined by the individual's response. [55] A recommendation that the response be evaluated after 1–3 months of steroid use has been made. [3] The steroids could also cause regression of the symptoms of hypercalcaemia, where present. [24] Seaworth [77] did not support the use of steroids solely for testicular sarcoidosis without any other systemic indications. Patel [78] had such a patient with only bilateral testicular lesions that regressed with the use of corticosteroids. Small, [79] while accepting that cortisone, a steroid, was an effective treatment option in sarcoidosis advised caution because of the risk of opportunistic infections like TB, due to the immunosuppression from its prolonged use. For the same reason, some practitioners administer Trimethoprim–Sulfamethoxazole alongside the steroids. [24] Steroid therapy in SOT leads to improvement of associated systemic sarcoidosis.

The effect of steroid therapy on testicular function and fertility is not known in the long run [26] but short courses have been shown to improve sperm counts. [55, 72] Incidences of natural fertilization following steroid use even in patients with OAT secondary to SOT have been reported [23] or of availability of sperm for assisted reproductive techniques in patients who were previously azoospermic. [59] In a case of infertility with no testicular mass, testicular biopsy confirmed a diagnosis of SOT. Steroid therapy led to restoration of spermatogenesis in that patient. A dose of 20 - 40mg per day is deemed sufficient but some start as high as 60 mg/d and taper it down over time. [71, 80]

It may be necessary to administer biphosphonates to reduce or prevent osteopenia from steroid- induced bone resorption. [72] They have also been reported to reduce granuloma formation. [81] A proton pump inhibitor should be added to combat the ulcerogenic side – effect of the steroids. [62]

SOT may present when patients are already being treated with steroids for extra-testicular involvement. [44, 82] This may constitute a dilemma as to what to do next. Methotrexate may be offered to those who do not respond to corticosteroids. [83] Anti-malarial medications like Hydroxychloroquine [84] and Chloroquine may be used. [12] HQ has been recommended for those with hypercalcaemia, neuro-sarcoidosis or skin nodules. [35] Minocycline, a tetracycline, is better for cutaneous and pulmonary involvement. It inhibits matrix metalloproteinases, apoptosis, angiogenesis and granuloma formation. [85] Other immunosuppressants like Azathioprine, [86] Cyclophosphamide or Cyclosporine are options of care. [12] Inhibitors of TNF – α (Tumour necrosis factor alpha) like Etanercept or Infliximab; Pentoxyfylline or Thalidomide have also been documented to hold potential use in sarcoidosis. [71, 87]

Surgical therapy

This may be a biopsy, testis–sparing or excisional surgery.

Biopsy: A biopsy should be via an inguinal approach [44]. It could be a frozen section biopsy (FSB) [88] or nodular excision. [59] As mentioned earlier, some authors recommend biopsies (open or FNAC) from more superficial extra–testicular sites. [10, 55] Kim [80] described in detail the use of an inguinal incision, and haemostasis with a rubber band tied around the spermatic cord, before taking a FSB. Khan [19] advocates that no biopsy is necessary.

Testis – sparing surgery: La Rochelle proposed criteria for offering a testis-sparing surgery to patients with SOT. These include African American descent, negative tumour markers and bilaterality. [76] These surgeries could include removal of a nodule, a partial orchidectomy, exploration of testis/testes and frozen section biopsy for histological confirmation of diagnosis or excision of largest lesion with preservation of the rest of the testis.

Complete excision: Documentation of orchidectomies and radical orchidectomies exist for SOT. This may be for the purpose of treatment or diagnosis.

The route of surgical intervention is important as the risk of up - staging a testicular malignancy must be kept in mind. An inguinal route is advocated. [81]

Description of the approach to the testis in SOT

The choice of anaesthesia may be local, spinal or general. An oblique skin crease incision is made in a line 2 cm above the pubic tubercle. This is deepened to the external oblique aponeurosis. The incision may be extended into the upper scrotum as deemed necessary. The scrotal contents may be delivered into the wound, gubernacular attachments divided, and the testis is isolated with drapes to permit a nodulectomy or partial orchidectomy. A tunica vaginalis incision is made and a biopsy taken or region excised between stay sutures.

The inguinal canal is opened to the internal ring for a radical orchidectomy, and the dissection extended 2 cm proximal to this. The vas deferens and vessels are individually ligated. A retroperitoneal dissection can then be done when deemed necessary.

Quantitative analysis of the cases reviewed

Methods

Various search engines (PubMed, Google, Google Scholar, Deepdyve. Science Direct, Wiley Online library, Research Gate, Academia.edu) were used to search for case reports and reviews on testicular sarcoidosis. Key words were “sarcoidosis”, “testis” and “epididymis”. The latter was included because of the possibility of dual involvement in individual patients. Cases that could not be validated by retrieval of the article or its abstract were excluded from the analysis e.g. the premier report by Nickerson. Google translate was used to facilitate translation of articles in Japanese, Portuguese, Mandarin and Spanish. Statistical analysis was with Statistical Package for the Social Sciences (SPSS) version 20.

Clinical presentation	Frequency	Percent	Valid percent	Cumulative percent
scrotal mass	44	62.9	65.7	65.7
constitutional symptoms	4	5.7	6.0	71.6
scrotal mass + constitutional symptoms	9	12.9	13.4	85.1
Other	10	14.3	14.9	100.0
Sub – total	67	95.7	100.0	
No information	3	4.3		
Total	70	100.0		

Table 2: Clinical presentations of patients with TS. (Others included arthritis, dactylitis, cough, lymphadenopathy etc)

Results

A total of 113 cases of sarcoidosis of the testis and epididymis were found. (72 were acclaimed to be reports of SOT). Information on the specific site involved could not be obtained for 3 reports due to lack of access to these reports. These were excluded. 40 (35.4) of which involved the testis alone. Thirty (26.5%) involved both the testis and epididymis, making a total of 70 cases of SOT. There were also 70 cases of SOE (40 of SOE alone). The mean age of the patients was 32.6 ± 10.62 years (median age was 30.5 years), ranging from 5 to 72 years.

The majority of the reports of SOT were from North America and among blacks (57.9%). Caucasians (21.1%), Asians/Middle East (17.5%) and Hispanics (2.9%) constituted the remainder. Fifteen

patients whose race could not be obtained were excluded from this analysis. Thirty two (45.7%) had bilateral lesions, while 27 (38.6%) had unilateral involvement. Contralateral testicular and epididymal involvement occurred in one case. Information could not be obtained for 10 (14.3) of the cases.

Most (84.2%) did not have a prior diagnosis of sarcoidosis. The lesions were more commonly painless (67.3%) and the most common presentation was a scrotal mass, as shown in Table 2. At least 50 patients (71.84%) had SOT as part of a multisystemic disease. (See Table 3 and 4) The average duration of symptoms was 4.67 ± 6.78 months. Six (8.6%), presented with infertility and two of whom had secondary infertility. Of the six, two had both epididymal and testicular involvement while the others had SOT alone. Incidentally, only three of these had documentation of abnormal seminal fluid analyses (SFA). The remainder of the SFA anomalies found in the review were incidental and not found during an evaluation for infertility. The SFA and testicular biopsies showed azoospermia, oligospermia, oligoasthenoteratozoospermia (OAT) with hypospermatogenesis and atrophic seminiferous tubules. Two other patients had hypogonadism with low growth hormone (GH) levels; and hypothalamic dysfunction. Due to the small number, regression analyses for bi-laterality, laterality or region of the testis, involved could not be run.

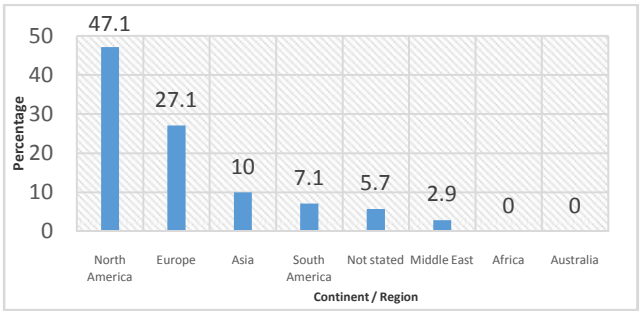

Chart 1: Percentage distribution of reports by continent or region

With regards the aetiology of SOT, two had a family history while two had autoimmune disorders (psoriasis and Grave's disease). Only one patient (1.4%) had a caseating granuloma (NSG). The rest were non–caseating granulomas.

There were seven (10%) with hypercalcaemia, two of whom were symptomatic. Two had raised LDH levels. Of the two, one had raised AFP and βHCG as well. Normal ACE levels were seen in 4 (5.7%) and calcium levels in 8 (11.4%). Nineteen (27.1%) had raised ACE levels.

The outcome of forty nine patients could be obtained. Thirty one (63.3%) had regression of the lesions, 10 (14.3%) had stable lesions, one each (1.4%) defaulted, experienced a recurrence, and had disease progression while on corticosteroids. Three (3) had no outcome stated while two died, with the diagnoses having been made at autopsy.

Table 3: A representation of the treatment options patients with TS received

Treatment offered	Frequency	Percent	Valid percent	Cumulative percent
None	5	7.1	8.8	8.8
Corticosteroids	26	37.2	45.6	54.4
Supportive care	1	1.4	1.8	56.2
Partial excision	2	2.9	3.5	59.7
Orchid-/ epididymectomy (O/E)	8	11.4	14.0	73.7
Radical orchidectomy	6	8.6	10.5	84.2
O/E+ steroids	7	10.0	12.3	96.5
Steroids + HQ	1	1.4	1.8	98.3
Steroids + Azathioprine	1	1.4	1.8	100.1
Subtotal	57	81.4	100.0	
No information	13	18.6		
Total	70	100.0		

Extra- testicular site	Frequency	Percentage
Chest	50	71.4
Epididymis	30	42.8
Eye	17	24.3
Skin	14	20
Spleen	10	4.3
Brain	7	10
Liver	6	8.6
Bones/Joints	4	5.7
Spine	3	4.3
Spermatic cord	2	2.9
Kidney	1	1.4

Table 4: Sarcoidosis affecting other sites in SOT

Scadding grade/ Pathology	Frequency	Percentage
0	10	14.3
1	10	14.3
2	15	21.4
3	3	4.3
4	1	1.4
Cavitations	1	1.4
Total	39	55.7

Table 5: CXR pathology in patient with SOT

Narrations of case reports and discussions

Do nothing – An option of care

The importance of patient choice in determining the line of management should never be overlooked.

Rao and Sabenegh [14] reported a case of right testicular and epididymal sarcoidosis in a 42 year old African American that started as a stable painless hemiscrotal swelling. An epididymal mass was palpated. The testis seemed normal. Months after no definitive treatment was received as desired by the patient, he represented with a nodular testicular mass. A chest X–ray showed bilateral hilar lymphadenopathy and paratracheal lesions. BAL and biopsy revealed sarcoid lesions. He received corticosteroids. The hilar deposits regressed. There was however testicular fibrosis. He refused surgical intervention.

Smyth [88] reported a case of a 25 year old white male with a painless right epididymal swelling that eventually involved the testis. The serial ultrasound showed a hypoechoic epididymal lesion that spread to the ipsilateral testis. There was pulmonary and hilar involvement. Testicular malignancy was ruled out serologically and a frozen section biopsy confirmed sarcoidosis. He received no treatment with a satisfactory resultant outcome.

Children with SOT

Reports in children are not common. Evans [37] reported a case in a 5 year old boy who had bilateral testicular involvement, as well as joint, skin and uveal affectation. Pena [56] and Zamora - Chanez [57] reported TS in 12 year olds.

Diagnostic dilemma

A case report by Eraso [46] highlighted the diagnostic dilemma experienced in a patient known to have sarcoidosis who develops a testicular mass. In the report, despite a negative assay for tumour markers, there was a solitary right testicular lesion with apparent capsular invasion on ultrasonography. The patient had an orchidectomy. Radical orchidectomies have been offered to some patients who eventually turned out to have sarcoidosis, due to the similarities borne to testicular malignancies. [91]A 31 year old white male with sarcoidosis confirmed from a right orchidectomy specimen had elevated βHCG and AFP levels, with no premorbid suggestion of a testicular tumour. Further against a testicular tumour was the presentation with pain, however, the patient was white. Caucasians have an increased risk of testicular malignancy so a consideration as to whether or not there was a rim of malignancy present was entertained, thus, necessitating the orchidectomy. This was refuted by histologic cross- examination. [16]

The possibility of cross-reactivity with sera or reagents used to rule out differential diagnoses, further worsens the dilemma. No documentation of a positive tuberculin test in a patient with sarcoidosis was found; however, a Mantoux reading of 2mm was reported. [86]Anergy is more often expected as seen in the case reported by Metcalfe. [93]A positive mumps test was also reported in one case.[94]

Subfertility and SOT

Reports while on treatment exist. A sad case was reported of a 34 year old man who had been on treatment for nasal, mediastinal, and cutaneous sarcoidosis, but was non- compliant. He had gained weight and had developed iatrogenic Cushing's syndrome from the steroids. He developed a left testicular mass after 7½ years of erratic therapy. He had a preceding documentation of a small penis and atrophic testes, worse on the right. With the development of the mass, his serum testosterone was assayed and found to be low (<20 ng/dl with reference values between 300 and 1200 ng/dl). He had a left orchidectomy. He had no child. [26]

Other reports of potential fertility issues have been documented. Testicular sarcoidosis was documented to cause oligoasthenoteratozoospermia (OAT) in a 23 year old Japanese with ophthalmic, pulmonary and testicular sarcoidosis. Seminal parameters improved with steroid use. [65]Rees [72] reported azoospermia in a 27 year old Caucasian who presented uveal sarcoidosis on topical care and developed bilateral testicular involvement later on. An open biopsy showed no spermatogenesis. His hormone profile was in keeping with hypogonadism and a semen analysis confirmed azoospermia. Following a 5 month course of high dose corticosteroids, there was some improvement in the sperm count, permitting sperm banking, and elevation of testosterone levels. Amenta [82] reported a case of bilateral testicular and epididymal involvement. The epididymides had rather normal ductules but the testes showed atrophic seminiferous tubules. Kovac [23] reported natural fertilization following use of corticosteroids by a patient with secondary infertility and seminal parameters of OAT from SOT. Paknejad [59] reported fertilization by assisted reproductive techniques (ART) in a patient who was azoospermic from SOT and was treated with steroids.

Myriad of presentations

A presentation of sarcoidosis with pain was reported by Rehman [74] who had a 29 year old man with right testicular pain, weight loss, and respiratory symptoms. Examination revealed a contralateral epididymal mass. Ultrasonography showed bilateral testicular involvement. Tuberculosis and a metastatic testicular tumour were ruled out. The author stated that the bilateral nature of the lesion reduced his suspicion of a malignancy. [74]The epididymal

involvement as well did not favour a testicular malignancy. [9]Lymphomas could be bilateral but the ultrasound would show "diffuse replacement".

The possibility of an asymptomatic nature of a testicular involvement was demonstrated when a 28 year old black man presented with a tender right epididymis. The testes were normal on palpation but ultrasonography showed multifocal right testicular lesions. [92]

A post-humus diagnosis of sarcoidosis affecting the testis, epididymis, heart, lung, liver, spleen and blood vessels of a 72 year old Japanese was made by Ishii and colleagues, [25] when the patient died of respiratory failure from what was assumed to be a Takayasu–like vasculitis that led to severe pulmonary arterial hypertension. Non-caseating granulomas were found in these organs.

Alraies [33] reported a case of a 37 year old black man with a three month's history of progressive paraparesis, urinary retention and impotence. (The nature of the impotence was not elaborated upon). He had a left testicular mass confirmed ultrasonographically, multiple left hemispherical and spinal lesions on MRI and a cavitary left lung lesion with mediastinal adenopathy, biopsy of which yielded necrotizing granulomatous pathology. Symptoms and lesions regressed with high dose CS therapy. NSG is rare, and even more rare in males. [32] This case report had affectation of the CNS which is a common site for it, [32] but was the first report of testicular NSG. [33] Rosen reviewed 214 cases of "NSG/nodular sclerosis" without documenting testicular involvement. [34]

A positive family history in first degree relatives was seen in two case reports. [84, 95]

Unresolved issues

Where there is a co-existing testicular and epididymal lesion, could the testicular lesion be deemed an extension of the epididymal lesion? Smyth [88] reported a case that suggested that with time the epididymal lesion progressed to involve the testicular lesion. In Burke's [96] report, the diffuse epididymal and multifocal testicular lesions were not contiguous. McWilliams [18] believes they are lesions of extension by contiguity.

Case reports from countries like Africa are sparse. This does not imply the disease entity is rare among Africans. Many of the studies documented in the European terrain record that the patients were of Nigerian origin. [62, 97] (One of them [62] had testicular involvement). A cross – sectional study of testicular biopsies in a Nigerian sub – population showed that 25% of the orchidectomy specimens for various indications, had granulomatous orchitis but no record of sarcoidosis. Granulomatous orchitis histologically has NCG in the interstitium of the testis alone. [41] It is difficult to differentiate from sarcoidosis lesions and some believe sarcoidosis to be a cause of GO. [98]

Conclusions

Sarcoidosis of the testis (ST) is not extremely rare. Clinicians need to be aware of the presentations clinical findings, investigations, and differential diagnoses as well as the treatment options of ST.

Conflict of interest: None

S.No	Reference	Age	Race	Presentation	Investigations	Treatment	Outcome	Comment
1	Rao PK, Sabanegh ES [14] 2009		African - American	Painless right hemiscrotal mass that gradually increased in size Late onset cough and low grade fever Past history of psoriasis	Bilateral hilar lymphadenopathy Testicular and epididymal involvement on scrotal ultrasound scan	Corticosteroids	Regression of hilar lymphadenopathy Persisting scrotal mass	Declined surgical intervention
2	Smyth [88] 2011	25	Caucasian	Painless right epididymal mass extending to testis	USS- epididymal mass invaginating into testicle CT thorax – pulmonary, hilar and mediastinal involvement FSB – NCG	None	Good	-
3	Alraeis [33] 2012	37	African American	Paraplegia Impotence Headaches	USS – Hypoechoic left testicular lesion CT chest – Lung cavitation and mediastinal adenopathy T1 MRI – dural and leptomemigeal hyper intense lesions	Corticosteroids	Improved muscle power Regression of CNS lesions	Caseating granuloma

4	Ishii[25] 2011	72	Japanese	Respiratory distress	CXR – cardiomegaly CT chest – centrilobular nodules Tuberculin test – Negative ACE – subnormal values	Respiratory support	Died Post – humus diagnosis	Subnormal ACE
5	Eyselberg[99] 2011	40	Caucasian	Right testicular swelling Cough, dyspnoea Skin lesions	USS – Hypoechoic lesion CXR – BHL + PI Abd CT – Splenomegaly, LN ACE - normal Negative TM + LDH LN biopsy – NCG	Corticosteroids	Regression	
6	Astudillo [54] 2004	28	African American	Bilateral testicular mass Skin lesions, uveitis Generalised LN	USS – hypoechoic testicular lesions with diffuse epididymal involvement Ga – scint- Hot spots in both testes; pulmonary involvement	Corticosteroids	Complete normalisation	
7	Hackney [26] 1986	34	African American	Known sarcoidosis. Non - compliant with CS. Recrudescent lesions Small testes and penis with left testicular mass 7.5 years after initial diagnosis	Ga scint- Hot spots in parotid, nose, lings Serum testosterone – Low	Left orchidectomy		Eunuchoid
8	Eraso [46] 1998	34	African American	Known sarcoidosis Rt testicular mass	USS – Apparent capsular invasion by solitary hypoechoic mass Negative tumour markers	Orchidectomy		
9	Burke [96] 1990	27	African American	Pulmonary and ophthalmic sarcoidosis Painless right hemiscrotal mass	USS – multiple hypoechoic epididymal and testicular nodules	Excision biopsy of a nodule		
10	Rehman [74] 2005	29		Rt testicular pain, fever and weight loss Cough, dyspnoea Incidental left epididymal swelling	USS – Bilateral testicular + Lt epididymal hypoechoic lesions CXR- bilateral PI Chest CT- BHI +cavitations FSB – NCG Tuberculosis, testicular tumours, fungalinvolvement and HIV were ruled out			
11	Corse[9] 1994	29	African American	Bilateral testicular masses Ciugh, dyspnoea Skin nodules Cervical + Axillary LN	USS – Bilateral multifocal testicular + Lt epididymal head hypoechoic lesions CXR- BPI + BHI + paratracheal nodes Chest CT – CXR findings + mediastinal node Negative tumour markers and AFB Skin and LN biopsy	Corticosteroids	Resolution of all lesions except left superior pole testicular lesion Excision biopsy of lesion undertaken – Sarcoidosis	
12	Maganty[92] 2008	28	African American	Tender right hemiscrotum Palpable epididymis	USS – Right testicular and epididymal lesions CXR – BHI	Excision biopsy of rt testicular nodules + rt epididymectomy	Regeression of pulmonary lesions	Would there have been resolution without the

								surgery
13	Frates [100] 1997	27	African American	Bilateral epididymal swelling Peripheral lymphadenopathy	USS – Bilateral testicular and epididymal diffuse hypoechoic lesions Lymph node biopsy – Sarcoidosis	Systemic therapy, not elaborated upon	Regression	
14	Frates [100] 1997	30	African American	Bilateral epididymal swelling Peripheral lymphadenopathy	USS – Bilateral testicular and epididymal diffuse hypoechoic lesions Lymph node biopsy – Sarcoidosis	Systemic therapy, not elaborated upon	Not known	
15	Thuret [16] 2008	31	Caucasian	Painful right testicle	USS – hypoechoic lesion CT- retroperitoneal solitary LN Elevated BHCG + AFP	Right orchidectomy	Resolution of retroperitoneal lesion Normalisation of tumour markers 3 weeks post op	
16	Takiguchi [65] 2008	23	Asian (Japanese)	Opthalmic sarcoidosis Incidental finding of bilateral testicular involvement	Ga scint – Widespread uptake, bilateral testicular uptake CXR – BHI + mediastinal widening Chest CT- As CXR both BPI Semen analysis - OAT Negative tumour markers, tuberculin test	Cprticosteroids	Gradual regression of lesions and improvement in seminal parameters	
17	Amenta [82] 1981	36	African American	Uveal and pulmonary sarcoidosis on corticosteroidsfor a year Left testicular followed by rt testicular painless swelling Epididymides enlarged as well	CXR – mediastinal LN Excision biopsy of left testicle and epididymis – NCG	No documentation of futher treatment	Not stated	Atrophic seminiferous tubules
18	Seaworth[77] 1983	29	African American	Left testicular and right epididymal involvement	CXR- BHI Syphilis, AFB, fungi, tumour ruled out FSB – granulomatous inflammation	Left orchidectomy		Contralateral involvement
19	Rutchik [91] 2001	31	African American	Skin lesions Dyspnoea Bilateral testicular masses Intraoperativ rt epididymal involvement	CXR – suggestive (No details) Negative Tumor markers Abdominal CT – Retroperitoneal LN Biopsy of lt testis	Radical right orchidectomy (larger testicle) Corticosteroids	Regression of left testicular lesion	Suspicion of malignancy
20	Opal [94] 1979	20	African American	Dyspnoea, cough Knee swelling Polydipsia, polyuria Bilateral testicular swelling	CXR – BHI + paratracheal LN Fungi, spirochaetes, AFB excluded Positive mumps test Norma testosterone Prolactin↑, TSH ↓ Excision biopsy right testicular nodule – NCG	Corticosteroids	Resolution	Hypothalamic dysfunction
21	Massarweh [75] 2006	24	Hispanic	Bilateral painful testicular swelling Weight loss	Chset CT- BHI Biopsy of testicular nodule – NCG AFB, fungi, malignancy ruled out	No treatment	Stable after two years	
22	Rees [72]2004	27	Caucasian	Uveal sarcoidosis	Semen –	High dose	Oligospermia	Potential male

				Bilateral testicular swelling	Azoospermia Hormone profile – Hypogonadism CXR – normal ACE ↑ Negative tumour markers Testicular biopsy – NCG	corticosteroids Biphosphonates	Sperm banking Regression in lesion size	infertility
23	Singer [60] 1990	29	African American	Eye involvement Right testicular mass Dactylitits Generalised lymphadenopathy	CXR – BHI + BPI + paratracheal LN + stranding USS – hypoechic lesion LN biopsy – NCG Negative tumour markers	Radical rt orchidectomy	Stable disease	
24	Strawbridge [101]	1990		One testis				
25	Bastion [86] 2007	24	Mongoloid	Red eye, diplopia Cranial nerve 3,5 - 8 palsies Scrotal swelling	MRI – Bilateral enlarged cavernous sinuses Mantoux – 2mm CXR – Normal Ca↑, ACE ↑, Globulin ↑ Negative TM Normal LDH AFB + Spirochaetes ruled out Testicular biopsy – NCG	Corticosteroids + Azathioprine		
26	Wason [102] 2010	46	Caucasian	Neurosarcoudsosis Painful ejaculation	USS – bilateral hypoechoic testicular lesions USS – guided core biopsies – epitheloidgranulomas Negative tumour markers			
27	Joel [103] 2014	27	Asian	Weight loss Lymohadenopathy	USS – hyperechoic lesions in left testis CXR – BHI + mediastinal LN CT chest – Suggestive of TB Bronshoscopy – NCG LN biopsy – No result AFB – Negative Orchidectomy specimen – NCG	Anti – TB drugs for 6 months Left inguinal orchidectomy Corticosteroids	Stable	Misdiagnosis of TB
28	Winter [6] 1995	38	Caucasan	Left hemi – scrotal swelling	USS – hypoechoic lesions CXR – PI CT – mediastinal LN = BHI FSB – NCG Splenomegaly Intra – op finding: epididymal involvement	No treatment offered as patient defaulted		
29	Hurd [104] 2000			Testicular swelling Nasal involvemnet	Biopsy – NCG			
30	Gross [105] 1992			Lacrimal gland Scrotal swellimg	Lacrimal gland biopsy – NCG	No further treatment	Stable 2 year F/U	No treatment
31	Gross [105] 1992			Scrotal swelling	Biopsy – NCG	No further treatment	Stable 10 year F/U	No treatment
32	Khan [19] 2004	35	Negroid	Submental masses Skin nodules	USS – Bilateral hydrocoeles with	Corticosteroids	Resolution of lesions and hydrocoeles	No biopsy taken

				Bilateral testicular swellings LN	hypoechoic nodules CXR – BHI CT – Normal ACE ↑ ESR ↑ Eosinophilia Negative TM			
33	Metcalfe [93] 1998	30	Negroid	Right epididymal swelling Cough, nightsweats	USS – hypoechoic lesions in both testes and epididymides CXR – BHI ACE ↑ Normal Ca Negative TM Anergy to Heaf test Rt orchidectomy specimen – NCG	Right orchidectomy Corticosteroids Triple therapy for TB		
34	SultanAli [106] 2005	30	Negroid	Painful left testis 2 week history of paraparesis Weight loss	USS –left epididymal mass CXR – Normal CT – BHI + MLN Spine MRI – T10 – 11 intradural extramedullary mass Negative TM TB ruledout Intra-op finding – Left testicular and epididymal mass Orhidectomy Specimen - NCG	Left orchidectomy Corticosteroids	Resolution of lesions Normal limb power	
35	Kim [80] 2011	27	Asian	Right testicular swelling Inguinal LN	USS – inf. Pole; Left varicocele CXR – Normal Abd CT – LN Tumour markers – Negative FSB – NCG	Corticosteroids Tapered down	Regression	
36	Woolf [62] 2010	50	Negroid	Cough Cervical LN Weight loss I yr later, left hemiscrotal mass	USS – hepatosplenomegaly; hypoechoic left testicular lesion CXR – BHL LFT – cholestasis LN + liver biopsy – NCG Negative TM Hypercalciuria Alk Phosphatase ↑	Left orchidectomy Corticosteroids	Regression	Epididymis and spermatic cord involved in orchidectomy specimen
37	Real [107] 2011	55	Caucasian	Known pulmonary sarcoidosis Scrotal swelling Weight loss	USS – bilateral testicular lesions CT chest/ abdomen/ pelvis - Normal Negative TM + LDH	Orchidectomy	Stable	
38	Iwasaki [108] 2009	47	Asian	Uveitis Scrotal swelling	CT – BHI + MLN Ga scint –Bilateral hot spots BAL- lymphocytosis	Epididymectomy + Testicular biopsy		
39	Esnakula [52] 2013	33	Negroid	Chest pain, cough Weight loss Scrotal mass including the scrotum Right inguinal LN	BAL – CD4:CD8 reversal CT – pleural effusion, BHI + PI ACE ↑ Negative TM + LDH Rt lung biopsy – NCG	Right radical orchidectomy Corticosteroids		
40	Zamora – Chavez [90] 2016	12	Hispanic	Erythhema nodosum Left hemiscrotal swelling LN Eye involvement	USS – Testicular and epididymal involvement, hydrocele CD4:CD8 reversal LN – biopsy ACE ↑ Negative TM Hypercalcaemia	Corticosteroids	Resolution	

41	Datta [81] 2006	38	Negroid	Bilateral painless testicular swelling Constitutional symptoms Generalised LN	USS – hypoechoic diffuse lesions CT – multiple LN ACE ↑ Negative TM Testicular biopsy – NCG	Anti – TB CS	REsolution	
42	Pena [89] 2005	12	Negroid	Arthritis Painful eye LN Bone involvement Let hemiparesis Painful left testis	USS – hypoechoic lesions Abd CT – LN LN biopsy – NCG Normal Ca Limb XR – osteopenia Negative TM	Left orchidectomy Corticosteroids	Regression	
43	Balaban[109] 2011	25	Mongoloid	Known pulmonary sarcoidosis Painful scrotal swelling				
44	Rees [110] 2004	27		Redeye Testicular swelling	USS – Bilateral hypoechoic lesions Serum testosterone, FSH, LH ↓ Testicular biopsy – Azoospermia	Corticosteroids	Improvement in sperm count	TS – induced Hypogonadism
45	Rees [110] 2004	31		Hypogonadism Rhinorrhoea	MRI – Hypothalamus involvement Hormone profile – Hypogonadism +GH↓	GH + testosterone replacement Corticosteroids Biphosphonates		
46	Kovac [23] 2013	37	Caucasian	Secondary infertility Hemoptysis Skin rash	CXR/CT- BHI + PI Semen analysis – Azoospermia Testicular biopsy - hypospermatogenesis	Corticosteroids	Improvement in sperm count to OAT	Intermittent boost in semen paramenters corresponded to time of use of steroids
47	PAtel[78] 2015	40	Negroid	Scrotal pain	USS – hypoechoic bilateral lesions CXR/ CT – BHI + PI + MLN + paratracheal LN Abd CT – REtrop LN FSB – NCG Normal ACE/LDH	Corticosteroids	Resolution of testicular masses Regression of pulmonary lesions	
48	Handa [38] 2003	25	Asian	Left hemiscrotal pain Uveitis LN Parotid Lungs Abdominal pain (symptomatic hypercalcaemia)	CXR –BHI + PI USS – diffuse testicular involvement. Hyperechogenic epididymides (epididymitis) T2 MRI – Bilateral epididymal and testicular lesions Ga scint – Hot spots in parotid, mediastinum, left hemiscrotum,hilar nodes ACE↑ Ca↑ Negative TM LN biopsy/ Bronchoscopy – NCG CD$:CD8 reversal	Corticosteroids	Resolution of lesions and abdominal pain	
49	Abusukheila [51] 2015	29	Caucasian	Mild testicular pain Fever, night	USS – Hypoechoic right testis + varicocele	No treatment	Stable	No treatment Smoker

				sweats, wt loss Cough	CT chest – PI + PTLN + Bud fashion ESR ↑, ACE ↑ Negative TM AFB ruled out			
50	Ghazle [84] 2011	Late 20s	Caucasian	Prior orchidectomy Left hemiscrotal pain Eye Skin Symptomatic hypercalcaemai	USS – Hypoechoic left testis; Normal epididymis with cysts CXR – BHL + MLN Ca↑ Negative TM + LDH Skin biopsy + orchidectomy specimen – NCG	Radical orchidectomy Corticosteroids + HQ		
51	Schechter [69] 1992	30	Negroid	Cough, fever, scrptal mass	USS – Superior pole lesion CXR – BHL + PI Abd CT – Splenomegaly ESR↑, ACE ↑, Globulin ↑ Negative TM Orchidectomy specimen – NCG	Radical orchidectomy Corticosteroids	Regression of cough	Suspicion of malignancy
52	Evans [47] 1997	5	Negroid	Joint pains Iridocyclitis Left facial nerve palsy Scrotal masses	CXR, Ca, ACE – normal ESR↑, IgG ↑ ACE ↑, Negative TM AFB and fungi ruled out Orchidectomy specimen – NCG	Left orchidectomy	The right testis became swollen after the orchidectomy	Sequential testicular involvement
53	Rohani [24] 2014	46	Negroid	Painful swollen scrotum Dyspnoea, cough, weight loss	USS – hypoechoic lesions CXR – BHL + PI Abd CT – LN ESR↑, ACE ↑, Ca - normal LDH ↑ Negative TM CD4:CD8 reversal Eosinophilia Transbronchial, skin, testicular biopsies – NCG	Corticosteroids Trimethoprim - sulfamethoxazole	Regression	Grave's disease Cocaine user
54	Verdecchia [111] 2008	36		Known sarcoidosis LN Right testicular swelling	USS – hypoechoic right testicular lesions LN + testicularbiopsy - NCG	No additional treatment		
55	Paknejad [59] 2011	42	Asian (Indian)	Bilateral testicular ain Cough, weight loss On steroids for sarcoidosis Infertile (Failed IVF)	Semen analysis – Progressive decline in semen count till he became azoospermic USS – heterogenous epididymis + hypoechoic testicular lesions CXR – Normal Chest CT – Hilar + MLN + PTLN ACE ↑, Ca - normal LDH ↑ Negative TM, BAL, AFB, Funal cultures	Corticosteroids	Improved sperm count that permitted Zygote intrafallopian transfer	
56	Ozguven [112] 1991	32	Negroid	Gait ataxia, paraparesis Skin lesions Weight loss Testicular swelling	USS – bilateral testicular lesions Ga scint – Uptake in skin, nose, right testis Brain MRI – Cerebellar lesions + hydrocephalus ACE, CXR – Normal	Right orchidectomy		
57	Bonachera [113] 1984			Lungs Intrathoracic LN	Testicular + epididymal			

					involvement			
58	Vasu [10] 2006	30	Negroid	Right hemiscrotal swelling Generalisd LN Splenomegaly	Uss – hypoechoic bilateral testicular and right epididymal lesions CXR – MLN + BHL + PI ACE ↑ Negative TM LN FNAC – NCG	Corticosteroids	Resolution of lesions	
59	Khan [19] 2004	35	Negroid	Painless bilateral testicular swelling Submental mass Weight loss, lethargy, night sweats Cervical LN	USS – diffuse testicular infiltrate, bilateral hydrocele CXR – BHI Chest CT – normal ESR ↑, ACE ↑ AFB, EBV, fungi ruled out Skin biopsy + FNAC submental mass - NCG	Corticosteroids	Hydrocoeles regressed	
60	Haas [114] 1986							
61	Khan MMHS [115] 2016	26	Negroid	Left testicular swelling Lungs		Corticosteroids		
62	Khan MMHS [115] 2016	31	Caucasian	LN Lung Liver Spleen Salivary gland, Bones	MRI – incidental finding of bilateral testicular lesions	Corticosteroids		
63	Khan MMHS [115] 2016	28	Negroid	Lung Neural Unilateral testicular swelling		Orchidectomy Corticosteroids		
64	Khan MMHS [115] 2016	32	Caucasian	Parotid LN Lugs Right testicular swelling	USS – hypoechoic lesion	Corticosteroids		
65	Uliaque [116] 2010	37		Bilateral testicular swelling	USS CT chest Ca ↑			
66	Kraus [117] 1958	41		Scrotal swelling Skin lesions	Right testicular involvement Epididymis CXR – BHL	Orchidectomy Epididymectomy		
67	Chowdhury [118] 1973			Scrotal swelling				
68	Longcope [30] 1952	34	Negroid	Known sarcoidosis Uveoparotid fever Haematuriia, polyuria Left facial nerve palsy and ptosis Skin lesions Cough, dyspnoea Died from uraemia	CXR – Grade II Hypercalcaemia, hyperphosphataemia Autopsy: Bilateral testicular involvement, kidney, epididymis, spleen, uvula, parathyroid gland, bone marrow			
69	Longcope [30] 1952	31	Negroid	Visual loss, Seizures, polyuria, weight loss, fever, Atrophic testicles, small prostate	LN biopsy – NCG Autopsy: Both testes, epididymis, lungs, tonsils, spleen, nasal mucosa, optic chiasm, pituitary, choroid, left fundus			
70	Turk [119] 1986							
71	Engleman [120] 1951	24	Negroid	Testis Epididymis	No histological confirmation			

				Uvea				
72	Kendig [15] 1974	!!	Negroid	Scrotal mass	Testicular involvement			

Table 5: Summary of the patients with TS. IgA: Immunoglobulin A; IgM: Immunoglobulin M; NCG: Non-caseating granuloma; CXR: Chest X-ray; MLN: Mediastinal lymph node; PTLN: Paratracheal lymph node; BP: Bronchopulmonary; BHI: HI: Hilar infiltrate; BHL: Bilateral hilar lymph node; Lt: left; Rt: Right; E: Epididymis; T: testis; ACE: Angiotensin-converting enzyme; AFB: Acid-fast bacilli; TM: Tumour markers; CT: Computerised Tomographic Scan; BAL: Bronchoalveolar lavage; LDH: Lactate dehydrogenase; IVF: In vitro fertilisation; Ga-67 scint: Gallium scintigraphy; MRI: Magnetic resonance imaging; USS: ultrasound scan; HIV: human immunodeficiency; TB: Tuberculosis; FSB: Frozen section biopsy; BHCG: β-human chorionic gonadotrophin; ESR: Erythrocyte sedimentation rate; FNAC: Fine-needle aspiration cytology; FDG-PET: Fluorodeoxyglucose positron emission topography; F/U: Follow-up; OAT: Oligoasthenoteratozoospermia; EBV: Ebstein - Barr virus.

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