



Sarcoidosis of Penis: A Review of the Literature

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Abstract

Sarcoidosis of the penis (SOP) is rare in view of this it would be expected that majority of clinicians would be unfamiliar with the disease. The aim of this article was to review the literature on sarcoidosis of the penis. Various internet data bases were searched including: Google, Google Scholar, Educus; and PubMed. The search words used included sarcoidosis of penis, sarcoid of penis, penile sarcoidosis. Sarcoidosis does affect the penis on rare occasions and this may mimic other diseases of the penis. Sarcoidosis of the penis (SOP) may present with penile swelling / induration; penile mass involving the external urethral meatus, glans penis or other parts of the penis; ulceration around the external meatus or ulceration elsewhere on the penis; bleeding mass on the external urethral meatus or elsewhere on the penis; a mass at the external urethral meatus with stenosis; a chronic abscess of the penis which may or may not be associated with a fistula; in some cases there may be a history of sarcoidosis elsewhere. Serum angiotensin converting enzyme level tends to be raised in 50% to 80% of cases. Diagnosis of SOP tends to be confirmed by histopathological examination features of the penile lesion. SOP may resolve following medical treatment with the use of steroids and some cases of SOP would require surgical treatment in the form of excision but some patients may require amputation operations of the penis and those who develop complications including meatal stenosis or abscesses would require further surgical treatment depending upon the type of complications they develop hence a long period of follow-up is required. SOP is a rare disease which may mimic other types of penile lesions and its diagnosis requires a high-index of suspicion. Treatment with steroids tends to lead to improvement of the lesions but surgical treatment in the form of amputation of penis and drainage of penile abscess and treatment of meatal strictures may be required.

Key Words: Sarcoidosis of penis; Serum Angiotensin Converting Enzyme; Amputation of penis; Penectomy; Prednisolone; Non Caseating granulomas; Schaumann body

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Introduction

Sarcoidosis is a multi-system granulomatous disease which has variable presentation, progression and prognosis. [1] Caesar Boeck in 1889 coined the

terminology sarcoid to describe a skin lesion of sarcoidosis because its histological examination features mimicked the histological characteristics of sarcoma [1] In 1905 Boeck described a number of patients who had sarcoidosis that presented with cough and nasal granulomas [1] In 1915 Kusnitski and Bittorf described chest X-ray abnormalities in a patient who had sarcoidosis [1].

Sarcoidosis of the penis is an extremely rare disease which may mimic a number of common and uncommon penile lesions. Early diagnosis of the disease would enable early appropriate treatment. The ensuing documentation on sarcoidosis of the penis is divided into two parts: (A) which contains an overview and (B) miscellaneous narrations and discussions from reported cases.

(A) Overview

Definition

Sarcoidosis is a benign inflammatory chronic non caseating multi-system disease of uncertain cause(s) [2] [3]

Epidemiology

○ It has been stated that sarcoidosis tends to be localized to the chest in 84% of cases [4]

○ It has been stated that Sarcoidosis affecting the genito-urinary tract occurs in 0.2% of clinically diagnosed cases and in 5% of cases of sarcoidosis diagnosed at autopsy. [5] [6] [7]

○ It has been reported that sarcoidosis affecting the genitourinary tract is ten times more common in black men [6]

○ Schaumann is credited with the report of the first case of sarcoidosis of the testis in 1936 [8]

○ It has been stated that sarcoidosis of the testis occurs most commonly in black men whose ages have ranged between 20 years and 40 years [9]

○ Vasu et al. [7] stated that in order of decreasing frequency sarcoidosis granulomas of the lower genito-urinary tract have been reported in epididymis, testis, and the prostate gland. Vasu et al. [7] further stated that sarcoidosis of the spermatic cord, scrotum and penis is rare.

○ Prevalence of sarcoidosis on the whole in the developed world is greater than 10 per 100,000 [3] However, sarcoidosis of the penis is not common

To the knowledge of the author less than 10 cases of sarcoidosis of the penis have been reported in the literature therefore one cannot make any categorical statements relating to the epidemiology of sarcoidosis of the penis.

Aetiology / Pathology

○ Mahmood et al. [3] stated that the aetiology of sarcoidosis is still not known; nevertheless, research suggests the possibility of a transmissible aetiology of the disease and perhaps a virus or a protoplasmic form of Mycobacterium tuberculosis as a possible cause of sarcoidosis. Mahmood et al. [3] further stated that studies which had used ultrasensitive PCR techniques to detect bacterial DNA in secretions had supported the possibility of tuberculosis aetiology in the pathogenesis of sarcoidosis.

○ Hassan et al. [10] on the other hand had summarized current postulates related to the mechanisms of sarcoidosis as follows:

➤ Shigehara et al. [11] had promulgated that active migration of CD4⁺ T cells and monocytes from the blood under the influence of different potent chemotactic factors, chronic disease which has been associated with tumour necrosis factor alpha, interleukin 8, and angiotensin-enzyme are associated with the development of sarcoidosis.

➤ Smith et al. [12] had suggested that a genetic predisposition to sarcoidosis is indicated in view of the findings of familial clustering, increased concordance in monozygotic twins, and susceptibility to the development of sarcoidosis among some ethnic groups, for example, HLA-DRB1 had been associated with African Americans and this had been linked to chromosome 5, and with German families and linked to chromosome 6.

○ Desmos [13] stated that the aetiology of sarcoidosis is unknown; nevertheless, evidence exists which would suggest that the pathological findings in sarcoidosis ensue an immunological problem hence it has been hypothesized that sarcoidosis is an emanation of unknown antigens, either non-self or self.

○ Desmos [13] described the inflammatory process of sarcoidosis with regard to immune response, granuloma formation, and tissue damage as follows:

➤ Immune response – Initially the acute inflammatory process associated with sarcoidosis fails to degrade the antigens and this is followed by non-specific chronic inflammation. Lymphocytes and mononuclear phagocytes next tend to be attracted into the area of inflammation, and furthermore migration of mononuclear phagocytes from the blood stream into the tissue in which they mature into macrophages and phagocytize the antigens as an attempt to neutralize them. The aforementioned cells form an important part in the development of noncaseating granulomas which form the histopathological hallmark of sarcoidosis. In sarcoidosis T-cell lymphocytes tend to be markedly increased within areas of active granulomatous disease and within these areas the ratio of T-helper cells to T-suppressor cells tends to increase markedly. This phenomenon is the opposite of the circulating blood in which the number of T-cells tends to be reduced and the ratio of T-helper cells to T-suppressor cells tends to be decreased. The

exaggerated T-cell activity is indicative of an altered immune response. The aetiology of the altered T-cell response is not known for certain; nevertheless, inherited or acquired alterations within the immune response genes may play a pivotal role or the antigen may affect the T-cell arm of the immune response selectively.

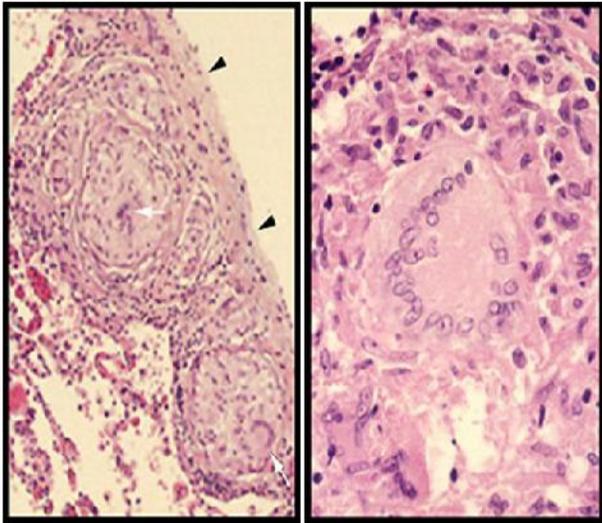


Figure 1 (Left): - Sub-pleural granuloma in lung. - These granulomas are in a typical position, adjacent to the pleura (arrowheads). Note giant cells (arrows) within central collections of epithelioid cells and the encircling rim of lymphocytes Reproduced from: Desmos T C. Image of Sarcoidosis – Pathology www.meddean.luc.edu/lumen/MedEd/Radio/sarc/SARCPATH.html. **Figure 1 (right)** Langhan’s giant cell. A Langhan’s giant cell in the central part of this granuloma is surrounded by epithelioid cells. Note peripherally arranged nuclei in giant cell.

➤ Granulomas – Microscopic examinations show that Granulomas are composed of a central collection of modified mononuclear phagocytes that are called epithelioid cells which are derived from macrophages (see figure 1 for an example of a sub-pleural granuloma for example of what a granuloma looks like on microscopy). When the macrophages develop into epithelioid cells they tend to gain secretory and bactericidal abilities but then they also tend to lose some of their phagocytic abilities. Microscopic examination of epithelioid cells tend to depict them as large, polygonal cells which have an elliptical nucleus that contain fine chromatin and one to two nucleoli and the cytoplasm of the epithelioid cells tend to be light or dark. Microscopic examination of granulomas, often tend to reveal giant cells in the central part of the granulomas. Giant cells are constituted by a number of epithelioid cells which

share the same cytoplasm and they tend to have large multiple nuclei. Initially, majority of the giant cells have nuclei that tend to be randomly distributed (foreign body giant cells) but subsequently the nuclei tend to be arranged in the periphery (Langhans type giant cell – see figure 2b for an example of a Langhans giant cell). The central epithelioid cells and giant cells tend to be surrounded by a rim of lymphocytes majority of which tend to be T-helper cells. The lymphocytes on microscopic examination tend to be seen as small, oval, basophilic cells with little cytoplasm. There is a phase called ‘naked granuloma’ during the initial stages of the formation of granuloma when there may not be any lymphocytes. Various types of cytoplasmic inclusion bodies could be associated with granulomatous inflammation including (a) laminated calcific Schaumann bodies, (see figure 3a for an example of Schaumann body) (b) stellate asteroid bodies, (c) and small oval brown Hamasaki-Wesserberg bodies. Even though the aforementioned inclusion bodies tend to be found in sarcoidosis there finding is not diagnostic of sarcoidosis.

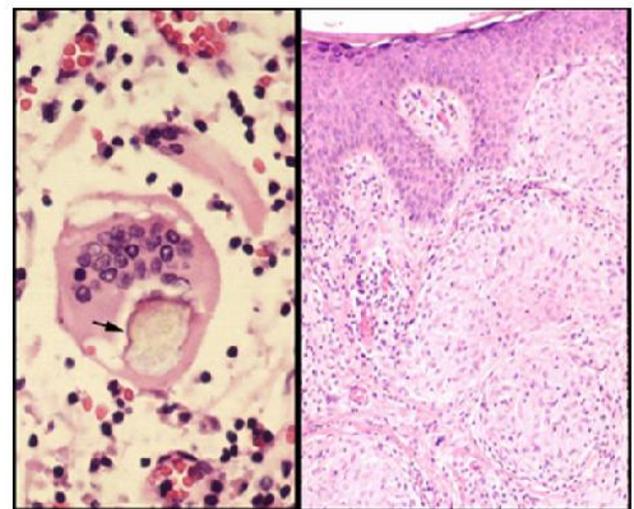


Figure 2 (Left): Cytoplasmic inclusion body - this cytoplasmic Schaumann body (arrow) is common in sarcoidosis but is not specific Reproduced from: Desmos T C. Image of Sarcoidosis – Pathology www.meddean.luc.edu/lumen/MedEd/Radio/sarc/SARCPATH.html] **Figure (Right):** Naked granuloma. - These young granulomas (arrows) in the skin have no surrounding rim of mononuclear cells and are called naked granulomas. Reproduced from: Desmos T C. Image of Sarcoidosis – Pathology www.meddean.luc.edu/lumen/MedEd/Radio/sarc/SARCPATH.html

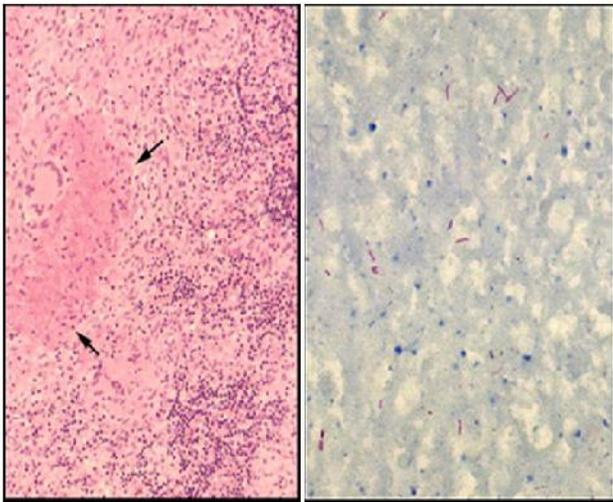


Figure 3 (Left): Cellular destruction in this tuberculous granuloma appears as clumped debris (arrows). This type of necrosis does not occur in sarcoidosis. Reproduced from: Desmos T C. Image of Sarcoidosis – Pathology www.meddean.luc.edu/lumen/MedEd/Radio/sarc/SARCPATH.html **Figure 3 (Right):** Caseous necrosis is most common in tuberculosis, but Gram negative, acid fast bacilli must be identified to make the diagnosis, as in this patient.

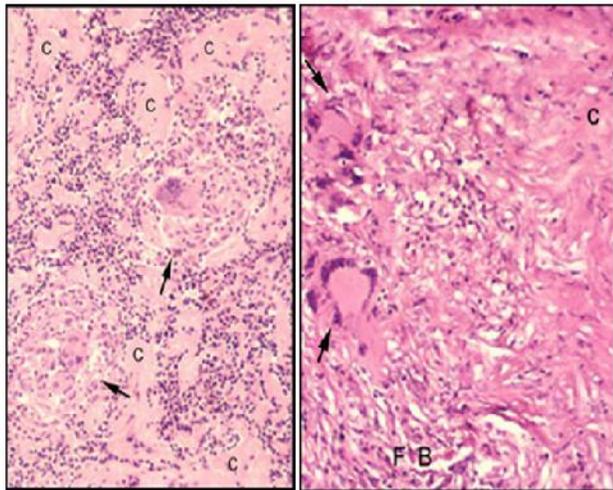


Figure 4 (Left): Early Collagen formation – Extracellular collagen (C) is being produced by fibroblasts which are difficult to see at this magnification. Reproduced from: Desmos T C. Image of Sarcoidosis – Pathology www.meddean.luc.edu/lumen/MedEd/Radio/sarc/SARCPATH.html **Figure 4(Right):** More advanced collagenous fibrosis – Elongated fibroblasts (FB) with more extensive collagenous fibrous tissue (C). Giant cells (arrows). Reproduced from: Desmos T C. Image of Sarcoidosis – Pathology. www.meddean.luc.edu/lumen/MedEd/Radio/sarc/SARCPATH.html

➤ Non-caseating granulomas – Sarcoidosis is typified by presence of non-caseating granulomas which differ from caseating granulomas that are

produced by other disease processes including tuberculosis. Caseous necrosis results from the destruction of cells that are converted into amorphous greyish debris which is found centrally within the granuloma. The terminology caseous (L. caseous, cheese) has been a coined terminology that describes the macroscopic appearance of caseous necrosis that mimics clumped, friable cheese (see figure 2 right which shows naked granuloma in comparison with figure 3 left which shows an example of caseous necrosis and figure 3 right which shows Mycobacterium tuberculosis in a specimen).

➤ Tissue damage – Damage to tissues and organs that ensues chronic inflammation tends to be an emanation of mass effect of granulomas on the anatomy of the tissues / organs and not a sequel of the release of mediators that damage the cells. Granulomas have the ability to resolve on their own or pursuant to steroid treatment. Resolution of a granuloma can be complete, it can leave an insignificant fibrous scar in the area of inflammation, or in the situation of chronic active disease there may not be a resolution of the lesion but rather more extensive tissue damage and fibrosis could develop leading to permanent organ dysfunction. In cases of extensive tissue damage and fibrosis fibroblasts tend to proliferate and they produce collagen and furthermore, the granulomas end up being enclosed by fibrous rings and which tend to be subsequently replaced by collagenous fibrous tissue (see figure 4 which show early collagen formation and more advanced collagenous fibrosis).

Presentation

Sarcoidosis is a multi-system chronic granulomatous disease and its presentation tends to be variable also tends to be related to sex, race and age. [10] Sarcoidosis may present asymptotically, or the symptoms may be vague and non-specific. Furthermore, the presentation of sarcoidosis does depend upon the organ system that is involved by the disease in that if the respiratory tract is involved there may be symptoms and signs related to the respiratory tract, if the eyes are involved by the disease there may be symptoms and signs related to the eyes, if the skin is involved there may be symptoms and signs related to the specific site involved, if the lymphatic system is involved there may be evidence of lymph node enlargement depending upon the nodes that are involved, the symptoms and signs on the whole tend to be related to the organs that are involved by the disease.

Sarcoidosis of the penis may present with

- (a) Penile swelling / induration
- (b) Penile mass involving the external urethral meatus, glans penis or other parts of the penis
- (c) Ulceration around the external meatus or ulceration elsewhere on the penis
- (d) Bleeding mass on the external urethral meatus or elsewhere on the penis
- (e) A mass at the external urethral meatus with stenosis
- (f) A chronic abscess of the penis which may or may not be associated with a fistula
- (g) In some cases of sarcoidosis of the penis there may be a history of sarcoidosis elsewhere but not always

Clinical Examination findings

- In cases of isolated sarcoidosis of the penis the general and systematic examination of the patient may be normal; however, examination of the penis may reveal an ulcer on the skin of the penis or on the external urethral meatus, or induration around the external urethral meatus, glans penis or any other affected part of the penis.
- In cases of systemic sarcoidosis associated with sarcoidosis there may be lesions on parts of the body affected some of which include: lymph nodes, skin, and the eye. Involvement of the lungs, liver, musculoskeletal system, the heart, the nervous system, the kidney and the gastrointestinal tract may not be clinically obvious in the first clinical examination or the clinical findings would not be specific to sarcoidosis.

Investigations

Haematological Investigations

Full blood count is undertaken as part of the general assessment of the patient but the results would not be specific for a diagnosis of sarcoidosis even in the presence of lymphocytosis which may reflect evidence of chronic inflammation.

Biochemistry investigations

Serum urea and electrolytes, bone profile and liver function tests.

- Serum urea and electrolytes as well as bone profile and liver function tests are investigations for the general assessment of patients with sarcoidosis. Serum Angiotensin Converting Enzyme (also called SACE or ACE) [14]
- SACE test tends to be requested to aid the diagnosis of sarcoidosis as well as in the monitoring of the disease. SACE tends to be elevated in 50% to 80% of patients who have sarcoidosis [14] but this would not specifically diagnose sarcoidosis of penis in that SACE levels could be elevated in sarcoidosis

of any organ. If SACE level is elevated in a patient with sarcoidosis, in that case SACE tests can be requested regularly at follow-up assessments as one of the methods of monitoring the course of the disease and response of the disease to corticosteroid treatment.

- ACE inhibitors are useful in the treatment of hypertension; however, they may interfere with the results of SACE tests undertaken for other reasons and knowledge of the fact that a patient is on ACE inhibitors for hypertension would be required in the interpretation of the relevance of the results of the SACE test. [14]

- Haemolysis and hyperlipidaemia may falsely decrease the concentration of SACE [14]

- Decreased concentrations of SACE may also be seen in patients who have the following: [14]

- Chronic obstructive pulmonary disease (COPD)

- Cystic fibrosis

- Emphysema

- Lung cancer

- Starvation

- Steroid therapy

- Hypothyroidism

- Moderate elevations of SACE levels have been found in various conditions including: [14]

- HIV

- Some fungal diseases

- Diabetes mellitus

- Hyperthyroidism

- Lymphoma

- Alcoholic cirrhosis

- Gaucher's disease (an inherited lipid metabolism disorder)

- Tuberculosis

- Leprosy

- SACE test is not used routinely for the diagnosis or monitoring of the aforementioned conditions because the use of SACE test has not been shown to be useful in the routine diagnosis and monitoring of these conditions. [14]

Other biochemistry tests

- Serum markers including: Serum amyloid A (SAA), soluble interleukin-2 receptor (SIL-2R), lysozyme, and glycoprotein KL-6 have also been reported by Miyoshi et al, [15] to be markers of sarcoidosis.

- It has been stated that hypercalcaemia or hypercalciuria does occur in non-caseating granulomas (NCGs) due to secretion of 1, 25, vitamin D, and that hypercalcaemia tends to be observed in 10% to 13% of patients with sarcoidosis, but on the

other hand hypercalciuria is 3 times more common. [16]

○ It has been reported that elevated levels of 1, 25, vitamin D, have been associated with protracted treatment of sarcoidosis and [16] serum 1, 25, vitamin D were found to be associated with patients who required repeated regimens of systemic immunosuppressive therapy or longer than one year of treatment. Seventy one percent of patients whose 1, 25, vitamin D levels, were higher than 51 pg/mL needed long-term immunosuppressive therapy [17].

○ It has been stated that in cases of sarcoidosis raised levels of alkaline phosphatase would be suggestive of liver involvement and Cremers et al. [18] had shown that the severity of abnormalities of liver function tests is significantly related to the degree of fibrosis and the extensiveness and degree of the granulomatous inflammation in sarcoidosis.

○ The aforementioned biochemical tests generally are descriptive features documented with regard to sarcoidosis but none of them is diagnostic of sarcoidosis of the penis.

Microbiology tests

Urine microscopy and culture is usually undertaken as part of the general assessment of patients with sarcoidosis of the penis but the results would not diagnose sarcoidosis. Sarcoidosis involving the external urethral meatus could cause urethral stenosis which could lead to difficulties in voiding as well as urinary tract infections. Urine culture and sensitivity tests would guide the clinician regarding the appropriate choice of antibiotics to treat penile sarcoidosis associated urinary tract infections.

Radiological Imaging tests

Chest X-ray

Chest X-ray may be undertaken in cases of sarcoidosis of the penis as part of the general assessment of the patient; however, in view of the fact that sarcoidosis is a multi-system disease chest x-ray undertaken as part of the general assessment could show lesions in thorax which could be contemporaneous sarcoidosis pulmonary or thoracic lesions. It has been stated that about 60% to 70% of patients who have sarcoidosis tend to have characteristic radiological imaging findings. [1] It has also been stated that, in between 25% and 30% of patients who have sarcoidosis the radiological imaging changes tend to be non-specific or atypical. [1] Furthermore it has been stated that in between 5% and 10% of patients with sarcoidosis the chest X-ray findings tend to be normal. [1] In cases of thoracic sarcoidosis the chest X-ray findings could be normal

but on other occasions there may be evidence of bilateral hilar and bilateral mediastinal lymph adenopathy which is not associated with any pulmonary abnormality. There could be other non-specific radiological imaging findings depending upon whether there is or there is no other respiratory tract pathology for example chest infection. Nevertheless the radiological findings on chest radiography would not be diagnostic of sarcoidosis. If there is an associated sarcoidosis of the chest the chest X-ray findings would depend upon the stage of the disease as follows: In stage O, the chest X-ray findings would be normal; In stage I, the radiological imaging would show evidence of lymphadenopathy only; In stage II the radiological imaging would show evidence of lymphadenopathy and pulmonary parenchymal disease; In stage III the radiological imaging would show only pulmonary parenchymal disease only; In cases of associated stage IV disease the radiological imaging would tend to show evidence of pulmonary fibrosis [1]

Ultrasound scan

Ultrasound scan of penis would reveal the position, size and extent of the penile lesion in sarcoidosis of the penis but the findings would be non-specific. Ultrasound scan of penis would also show whether or not there is thrombosis of corpus cavernosum in association with the penile lesion in sarcoidosis of the penis.

CT-Scan

CT scan of thorax, abdomen, and pelvis may be done as part of the general assessment of the patient with sarcoidosis of the penis. The CT scan would show whether or not there is a contemporaneous / synchronous sarcoidosis lesion anywhere else in the thorax, abdomen or pelvis. The CT scan would also define the extent, position and size of the penile lesion. In cases of associated thoracic sarcoidosis The CT scan features would depend upon the stage of the associated disease and these may be normal, or there may be evidence of nodules or nodes in the hilar, mediastinum or within the lungs or there may be evidence of pulmonary fibrosis. It has been stated that CT scan is more sensitive with regard to detection of mediastinal lymphadenopathy. High resolution CT scan (HR-CT) tends to show subtle parenchymal lung disease which ordinary plain x-ray may not show. [1] Furthermore early acinar patterns, nodules of the parenchyma, and nodular consolidations tend to be more clearly defined on HR-CT in comparison with plain chest X-ray [19], [20], [21], [22], [23], [24]. In associated

pulmonary sarcoidosis HR-CT scan may show: areas of ground-glass attenuation; sub-pleural nodules; perivascular nodules which tend to be depicted as beading and irregular thickening of bronchovascular bundles; as well as thickening of interlobular septa. [1]

MRI scan

MRI scan of thorax, abdomen and pelvis is an alternative radiological investigation to assess a patient with sarcoidosis of the penis to exclude a sarcoidosis lesion elsewhere. MRI scan has an advantage in that there is no radiation involved and therefore there would be no worries relating to cumulative radiation effect with subsequent further imaging. MRI scan is helpful with regard to characterization of bony involvement of sarcoidosis with particular reference to sarcoidosis of spine [1] [25]

Nuclear Imaging

Isotope imaging is not used in the diagnosis of sarcoidosis of the penis but it can potentially be used as part of the general assessment of a patient with sarcoidosis of the penis to ascertain whether or not there is a sarcoidosis lesion elsewhere. It has been stated that Gallium-67-avid disease has been reported in 90% of pulmonary sarcoidosis. [1] In view of this it could be said that this type of scanning when used as part of further assessment of a patient with sarcoidosis of the penis could indicate presence or absence of pulmonary sarcoidosis. It has also been stated that a lambda pattern of radio-nuclear uptake in the infra-hilar, para-hilar, broncho-pulmonary, as well as in the mediastinal lymph nodes had been documented in 72% of patients afflicted by intrathoracic sarcoidosis. [1] Furthermore, it has been stated that symmetrical radioisotope uptake does occur in 79% of patients who have sarcoidosis of parotid gland and lacrimal gland. [1]. The aforementioned statements would indicate the potential usefulness of nuclear imaging in the assessment of patients who have sarcoidosis of the penis to exclude sarcoidosis lesions elsewhere.

Whole body FDG-PET scan

It has been documented that with regard to sarcoidosis, the use of positron emission tomography (PET), scan together with fluorine-18 fluorodeoxyglucose (FDG) does have a role to play in the detection, identification of accessible sites of biopsy, quantification of the activity of the disease, outcome prognostication of the disease, as well as assessment of response. [1] [26]

Pathology features

Macroscopic features

(a) The characteristics of penile sarcoidosis lesions are not specific or diagnostic of sarcoidosis. There may be induration of the penis; there may be a mass or nodule on the penis; there may be ulceration on the penis or external urethral meatus associated with a visible or palpable mass; the penile lesion as it progresses may be associated with a chronic abscess or fistula.

(b) In the situation where there is sarcoidosis involving other organs then there may be evidence of other lesions in the affected organs.

Microscopic features

Sarcoidosis is associated with the development of chronic non-caseation granulomas and this may mimic other types of chronic granulomas. A number of chronic granulomas tend to have different types of inclusions and their identification is useful in differentiating sarcoidosis from other types of granulomas

Microscopic examination of features of sarcoidosis lesions have been summarized as follows: [27]

(a) Presence of inflammatory and granulomatous reactions associated with dense superficial and deep lymphocytes, eosinophils as well as plasma cells

(b) Presence of parakeratosis spongiosis, acanthosis and epidermal erosion which is usually variable

(c) There may be presence of lymphoid germinal centres which simulate lymphoma associated with destructive adnexa and atypia

(d) Presence of non-caseating granulomatous infiltrate, which usually tends to be dense in the dermis and tends to extend into the subcutaneous fat. The granulomas tend to be discrete and uniform with regard to size and shape and furthermore, they also tend to be comprised of epithelioid histiocytes which contain abundant eosinophilic cytoplasm and oval-shaped nuclei which contain small central nucleoli. Presence of variable amounts of Langhans giant cells and lymphocytes which tend to be scattered.

(e) Presence of discrete small central foci of fibrinoid necrosis may be observed as well as trans-epidermal elimination

Calcium oxalate crystals, H&E

Calcium oxalate crystals – polarized

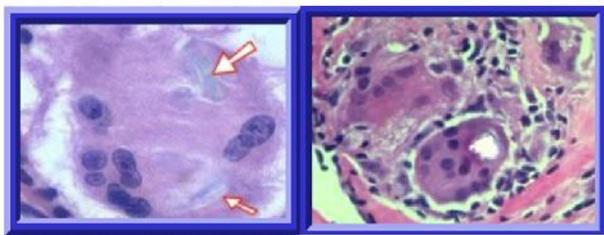


Figure 5: Crystalline Inclusions: Colourless refractile crystals composed predominantly of calcium oxalate are frequently found in the giant cells of granulomas of sarcoidosis and other diseases. In some cases they may serve as the nidus for deposition of calcium leading to formation of Schaumann (conchoidal) bodies (Reproduced from: Rosen V (Vale) inclusions in granulomas Schaumann (conchoidal) bodies Atlas of Granulomatous diseases URL: granuloma.homestead.com/inclusions.html under copy right which states that the images may be copied and utilized for education or other non-commercial purposes. Copyright is still maintained by Vale Rosen who has granted permission for the figures to be used for this article on this occasion only for non-commercial use and to reproduce these figures Vale Rosen would need to be contacted.

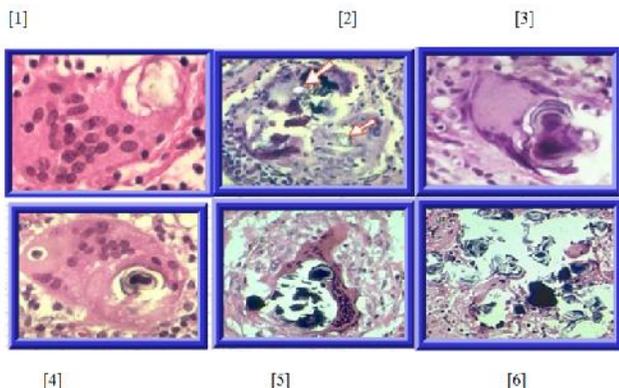


Figure 6: Schaumann (Conchoidal): Large concentric calcifications often containing refractile calcium oxalate crystals (figures 1-6) Although usually intracytoplasmic, they may if numerous or very large, be extruded into the extracellular space (see figure 6 above) Reproduced from: Rosen Y (Yale) inclusions in granulomas Schaumann (conchoidal) bodies Atlas of Granulomatous diseases URL: granuloma.homestead.com/inclusions.html under copy right which states that the images may be copied and utilized for education or other non-commercial purposes. [1] Early Schaumann body forming around calcium oxalate crystals; [2] Fragmented Schaumann body surrounding calcium oxalate crystals (at arrows) polarized; [3]. Schaumann body [4] Schaumann body [5] Large fragmented Schaumann body [6] Extracellular Schaumann body. Copyright is still maintained by Vale Rosen who has granted permission for the figures to be used for this article on this occasion only for non-commercial use and to

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(f) Presence of (i) Schaumann bodies (a terminology which is used for calcium and protein inclusions within Langhans giant cells that is part of a granuloma; basophilic laminated rounded conchoidal structures), (ii) asteroid bodies (small, intracytoplasmic eosinophilic star shaped structures which also tends to be present in tuberculoid leprosy, berylliosis and atypical facial necrobiotic xanthogranuloma), (iii) Hamazaki Wessenberg bodies (a terminology used to describe peculiar PAS positive inclusions which may be large lysosomes that contain hemolipofuscin.

It has been stated that presence of foreign material in sarcoidal granuloma does not exclude sarcoidosis. [27]

Differential Diagnosis

Some of the differential diagnoses of sarcoidosis of penis include various granulomatous diseases such as:

- (a) Tuberculosis [27]
- (b) Leprosy [27]
- (c) Berylliosis [27]
- (d) Fungal infection [27]
- (e) Crohn’s disease [27]
- (f) Foreign body granuloma [27]

Considering the fact that sarcoidosis of the penis tends to present as penile lump, induration and penile ulcerations of long durations of time penile malignancies should be considered in the differential diagnosis.

Treatment

Medical Treatment

- Sarcoidosis generally can be treated by using topical and or systemic steroids. Limited evidence based upon the few reported cases would indicate that some sarcoidosis lesions of the penis may initially respond to steroid treatment but the lesions may subsequently recur as well as progress in view of this it is important that all patients with sarcoidosis of the penis should be followed so that if there is evidence of recurrence or progression of the disease then other treatment options should be undertaken.
- Hassan et al. [10] stated that with regard to treatment of sarcoidosis the first line choice of treatment is corticosteroids which should be used for a period of 12 months; nevertheless, in situations of patients with sarcoidosis experiencing repeated relapses of their sarcoidosis disease would tend to require long-term, low-dose corticosteroid treatment.

Chemotherapy

Chemotherapy was used in the treatment of one patient who had progressing disease which did not result in resolution or improvement of the sarcoidosis penile lesion. In view of the very few reported cases of sarcoidosis of the penis one cannot at the moment say categorically whether or not chemotherapy may be useful in the management of sarcoidosis of the penis.

Radiotherapy

Chemotherapy and Radiotherapy have been used in the treatment of recurrent/persistent sarcoidosis of penis following initial partial amputation of the penis without any response which required subsequent total penectomy and construction of perineal urethrostomy which eventually cured the lesion. There is also a report of the use of radiotherapy in the case of recurrent sarcoidosis of the penis which was curative. There is no consensus opinion regarding the place of radiotherapy in sarcoidosis of the penis. There is also no way of predicting which cases of sarcoidosis of the penis that would respond to radiotherapy. Considering the fact there has been previous documentation of response to radiotherapy of a sarcoidosis lesion that recurred after partial amputation of penis, it would be reasonable to offer patients whose sarcoidosis of the penis have recurred after partial amputation of penis and to closely follow them up to assess the response to treatment.

Surgery

Possible surgical options of treatment include:

- Complete excision of the penile lesion if the lesion is small and can be excised completely with no residual lesion (this would constitute excisional biopsy of the lesion for histological diagnosis).
- Partial amputation of penis with complete excision of the penile lesion.
- Extensive lesions may require total penectomy and perineal urethrostomy.
- Urethral dilatation as treatment for urethral stricture may be required if the penile meatal lesion is associated with urethral / meatal stenosis

Other miscellaneous forms of treatment

○ Hassan et al. [10] had stated that with regard to patients with sarcoidosis in general who have had unsatisfactory response to corticosteroid treatment or in the cases of patients who have required high doses of corticosteroids then other options of treatment documented by Slovakova et al. [28] include immunosuppressive therapy, cytostatic therapy, antimalarial treatment, treatment with tumour

necrosis factor inhibitors, treatment with pentoxifyllin, treatment with infliximab, treatment with adalimumab, and treatment with leflunomid.

○ Whilst the aforementioned other treatment options have been used in managing sarcoidosis affecting some organs, there are no reports of such aforementioned treatment options in managing sarcoidosis of the penis.

Outcome

Generally, the outcome of sarcoidosis tends to be variable; but the disease has a tendency to wax and wane in its manifestations which tend to correlate its mode of onset and the extent of the disease. [10] It has been stated that with regard to sarcoidosis generally, sarcoidosis with acute onset manifestations with erythema nodosum or asymptomatic bilateral hilar lymph node enlargement tend to be associated with a self-limiting course with spontaneous resolution, but sarcoidosis with insidious onset with pulmonary involvement or multiple extra-pulmonary lesions, may be ensued by progressive lung fibrosis and other organ involvement. [10]

Sarcoidosis lesions of the penis may respond initially to steroid therapy (topical / systemic) but the lesion may subsequently relapse following which surgical treatment of partial amputation of the penis may be required. Recurrence or further progress of the disease may occur after partial amputation which may require treatment by means of radiotherapy or total penectomy. It is not clear whether or not radiotherapy as primary treatment of the disease in combination with steroid treatment would provide adequate treatment after the diagnosis has been made following biopsy of the lesion in order to avoid partial or total penectomy. One case has been reported of complete response to radiotherapy after recurrence of sarcoidosis following partial amputation and one case has been reported when both radiotherapy and chemotherapy did not resolve a recurrent penile sarcoidosis following partial amputation of the penis and the patient required total penectomy. Few cases of sarcoidosis have been reported and there is no way one can predict which lesions would respond to treatment and which lesions would progress. In view of the unpredictable biological behaviour of sarcoidosis of the penis, all patients with the disease must be carefully followed-up and clinicians should be encouraged to report cases of sarcoidosis of the penis they encounter as well as the treatment and outcome so that the biological behaviour of the lesion can be ascertained to enable a consensus opinion to be made regarding the treatment options of the disease.

(B) Miscellaneous narrations and discussions from some reported cases

In 1941 Longcope reported the first case of sarcoidosis which affected the skin of the shaft of a black man's penis [29] and in 1942 Longcope and Fisher [30] again reported the case of sarcoidosis which had affected the skin of the black man's penile shaft. It was reported that an apparently healthy 40-year-old black man died suddenly and as a result of the death a post-mortem examination was undertaken. The post-mortem examination showed enlargement of lymph nodes (a) in the mediastinum, (b) mesentery, and (c) retroperitoneum. Microscopic examination of biopsy specimens obtained from multiple sites showed features of sarcoidosis in large masses that had surrounded the great vessels of the thorax, and had infiltrated the pericardium, the lungs, liver, kidneys, spermatic cords, cerebral dura, as well as the skin of the penis.

Carli [31] in 1955 reported the second case of Boeck-Schaumann of the balanoprepucial sulcus. Carli [31] reported a 28-year-old white man who presented with a painless pink nodule on his balanoprepucial sulcus. The nodule measured 0.5 cm and its centre was found to be ulcerated and its edge felt hard on gross examination. Microscopic examination of the nodule showed non-caseating sarcoidosis granulomas within the dermis associated with occasional giant cells. Carli [31] also reported the finding of multiple satellite nodules and bilateral inguinal lymph node enlargement were also found in the patient.

Vitenson and Wilson [32] in 1972 reported a 29-year-old black man who presented with painless swelling of his anterior cervical nodes in February 1965. He had a chest X-ray which showed widening of his mediastinum. As part of his investigation he had biopsies of the liver, lung and kidney and histological examination of the specimens showed granulomatous inflammation which was adjudged to be consistent a diagnosis of sarcoidosis. He had a number of investigations which included (a) 24 hour urine protein of 3.9 grams, (b) serum alpha 2 which was elevated (c) gamma globulins were elevated. He was discharged home on prednisolone 60 mg daily and two months later his 24-hour urine protein had decreased to 55 mg and the prednisolone medication was gradually withdrawn. Three months after his presentation he was found to have an elevated blood pressure of 190/130 mm Hg and he was temporarily treated with an-antihypertensive medication which brought his diastolic blood pressure down to between 90 and 100 mm Hg. Three years and 3 months (39 months) after his initial presentation he re-presented

with visible haematuria. He had excretory urogram which was normal. He underwent cystoscopy which showed submucosal cysts within the urinary bladder neck and trigone which was considered to be suggestive of cystitis cystica and this was treated with sulfisoxazole for a period of 10 weeks. He underwent follow-up cystoscopy 17 months later (40 months after his initial presentation) which was normal showing resolution of the cystitis cystica. Five years and ten months (70 months) after his initial presentation he presented again with a painless mass which had been growing on his penis for eighteen months. On the whole his general and systematic examination was unremarkable except for patches of discrete, pale-yellowish, painless nodules which were waxy in appearance were found on his right elbow, left knee and anterior aspect of his leg. On his glans penis, similar nodules were found to the left side of his external urethral meatus and a nodule was also found contiguous to the right side of the external urethral meatus. The penile mass was excised and gross examination of the specimen showed a firm, light-yellowish waxy mass that had distinct borders and measured 2 cm x 2.5 cm. Microscopic examination of the specimen did show that the epidermis was flat and the dermis had contained 2 giant cells which were surrounded by many, non-caseating granulomas consistent with the diagnosis of sarcoidosis involving the glans penis.

Whittaker et al. [33] in 1975 reported a case of sarcoidosis of the penis in a patient who presented with ulceration of the external urethral meatus. Whittaker et al. [33] reported a 59-year-old Welsh laboratory technician who in May 1971 had presented with mild blood stained urethral discharge and mild pain within his external urethral meatus on voiding. Eight years prior to his presentation (1963) he had undergone excision of an enlarged submandibular lymph node histological examination of which had shown a typical sarcoid granuloma Four years prior to his presentation he had undergone trans-urethral resection of prostate and histological examination of the specimen had confirmed benign prostatic hyperplasia but he subsequently developed bladder neck stenosis which required further trans-urethral resection of prostate. At his presentation in 1971 he was found to have phimosis otherwise his examination was normal. He underwent examination under anaesthesia which revealed an irregular ulcerated tissue in/around his external urethral meatus. He had biopsy of the tissue and histological examination of the specimen showed features of non-specific granuloma. He developed over the ensuing 8 weeks, the ulcerated area around his external urethral

meatus, in view of this a circumcision was performed as well as another biopsy was taken of the ulcerated lesion. He underwent cystoscopy which showed a normal urethra and urinary bladder. Histological examination of the second biopsy specimen was adjudged to have shown follicular non-caseating granuloma with giant cells which was consistent with a diagnosis of sarcoid. At that time a skin lesion was noted in his anterior chest wall and this was excised and histological examination of the specimen showed features that were similar to the histological features of the penile biopsied lesion. He had a number of investigations which were reported as follows:

- Full blood count, serum electrolytes, proteins, calcium and phosphates – normal; erythrocyte sedimentation rate 55 mm per first hour.
- The Wassermann reaction GCFT, VDRL, Bacterial and viral studies, chest X-ray – normal
- Mantoux test weakly positive at 1 : 1,000
- Kveim test carried out after steroid therapy – negative (interpreted as perhaps negativity due to suppression by steroid therapy).

He was treated with prednisolone 30mg daily for the first month and this was reduced to 20 mg per day. Within a period of two months the penile ulceration had healed but a meatal stricture developed which required meatoplasty. Twelve months following his initial presentation he developed pain in his glans penis as well as soreness in his urethral meatus. He developed tenderness and induration of his glans penis as well as scabbing at his external urethral meatus. He subsequently developed two further ulcers on his glans penis. He next underwent partial amputation of the penis from which he initially recovered well. Histological examination of the partially amputated penis showed chronic abscess formation deeply seated in the glans penis. One month after the partial penile amputation he presented with intermittent bleeding from the amputation site and on examination an ulcer was found at the cut ends of the corpora cavernosa. A biopsy was taken of the lesion and histological examination showed chronic inflammatory cell infiltrate mainly lymphocytic infiltrate. He was next treated by means of external beam radiotherapy and the penile ulceration healed after that. The steroid therapy was stopped 3 months after he had completed the radiotherapy treatment. The ulcer had remained healed and he was voiding well two years and five months after his initial presentation with his penile lesion. Nevertheless, the patient did develop severe osteoporosis of the dorsal spine and had been wearing a spinal support as well as had been receiving calcium supplements and vitamin D. With

regard to the case Whittaker et al. [33] were of the opinion that their case mimicked carcinoma which had to be excluded by means of biopsies taken on two separate occasions. With regard to the aetiology of the sarcoidosis in their case they had considered the possibility of local trauma which had been induced during the patient's previous trans-urethral resection of prostate as a possible factor responsible for the initiation of the sarcoidosis; nevertheless, the long-time interval of 4 years between the second trans-urethral resection and the appearance of the sarcoidosis would not be in support of the local trauma postulate as a cause of the sarcoidosis. On the other hand, presence of multiple skin lesions and the previously excised sarcoidosis involved submandibular gland would provide evidence to support systemic sarcoidosis postulate as the reason behind the sarcoidosis of the penis. With regard to treatment of sarcoidosis, Whittaker et al. [33] stated that on the whole radiotherapy had been previously considered not to be effective in the treatment of sarcoidosis lesions based upon the fact that firstly, in 1942 Bernstein and Oppenheimer [34] did report encouraging results in relation to radiotherapy treatment of 4 cases of sarcoidosis, Donlan [35] in 1948 had reported that out of 11 cases of sarcoidosis lesions that were treated by means of radiotherapy only one had shown any improvement.

Rubinstein et al. [36] in 1986 reported a case of sarcoidosis of the penis in a patient who had presented with chronic painful erythematous induration of the penis associated with many subcutaneous nodules and cutaneous ulcerations. Rubinstein et al. [36] reported that the penile lesions improved in response to the application of topical steroids but the lesions subsequently reappeared and persisted despite further treatment with topical steroids. Rubinstein et al. [36] stated that despite the fact that sarcoidosis is not common sarcoidosis should be considered in the differential diagnosis of any chronic lesion which has involved the penis.

Mahmood et al. [3] in 1997 reported a 67-year-old man who presented with urethral bleeding as well as dysuria. Several years preceding his presentation he was diagnosed with sarcoidosis with cervical lymphadenopathy. On examination he was found to have an irregular haemorrhagic ulcerated lesion around the external urethral meatus. He had cystoscopy which revealed a normal urethra and normal urinary bladder. Histological examination of biopsy specimen of the external urethral meatus penile lesion showed non-caseating granulomas which consisted of epithelioid cells and Langhan type giant cells which were reported to be diagnostic of

sarcoidosis. He was started on systemic steroid treatment which resulted in transient improvement of the lesion. He subsequently developed meatal stricture which required meatal dilatation, and involvement of the foreskin which was treated by circumcision. The ulcerated lesion further progressed in view of which partial amputation of the penis was undertaken. Pursuant to his amputation of the penis the patient developed an abscess which had involved the base of the penis associated with a fistula. He was treated by means of radiotherapy and chemotherapy without any success. He next underwent total amputation of penis and construction of a perineal urethrostomy. The disease did not progress further pursuant to the total amputation of the penis. Mahmood et al. [3] stated the following:

) Sarcoidosis is associated with a fairly unpredictable course.

) The genital organs tend to be involved in the second subacute stage of sarcoidosis.

) Rubinstein et al. [36] had intimated that sarcoidosis lesions tend to heal within 6 months to 3 years by fibrosis or hyalinization.

Mahmood et al. [3] advised that sarcoidosis should be considered in the differential diagnosis of penile ulcers.

Wei et al. [37] in 2000 reported a 31-year-old African American man who presented with lesions on his penile skin and scrotum which had been present for a period of two years. The genital lesions had interfered with his sex life. Histopathological examination of biopsies of the lesions confirmed a diagnosis of sarcoidosis.

Rustscheff [38] reported a 57-year-old Caucasian man who had presented to the emergency department in 1980 and 1990 because of a swelling of the shaft of his penis. On each of the two occasions a diagnosis of penile thrombosis was made

after he had had ultrasound scan of the penis and he received heparin treatment for 3 months. In 1990 he was diagnosed with Lofgren’s syndrome but this did not require any sarcoid-specific treatment. He subsequently developed schizophrenia and in 2001 he presented with a growth on the shaft of his penis. The growth was excised and histological examination of the specimen showed non-specific inflammation. He developed pericarditis in 2002 and both his penile lesion and schizophrenia had also progressed. He also developed a new thrombosis which was confirmed by means of ultrasound scan of the penis which did show his corpus cavernosum to be filled with material of medium ecogenicity. He developed progressive swelling of his right corpus cavernosum for which on many occasions he had biopsies of the swelling and pathological examination showed noncaseating granulomas and epithelioid cells in 2009. He had computed tomography scan of the thorax, abdomen and pelvis which did show enlarged inguinal glands and basal fibrosis. Pathological examination of the lesion in the beginning, showed features which were adjudged to be consistent with sarcoidosis but this diagnosis was subsequently revised and a diagnosis of lipogranuloma and foreign body reaction was said to the diagnosis. He later on, developed urethral stricture and fibrinous ulcers on his glans penis. Sexually transmitted disease and tuberculosis had been excluded. He had serological tests which showed high levels of ACE, beta-2-microglobulin, and low levels of 25-OH-D3. He had not received any sarcoidosis specific treatment until August 2013. He was commenced of 20 mg of prednisolone treatment and within 6 weeks his lesions had completely resolved. Rustscheff [38] stated the following: sarcoidosis is a disease of protean presentations and the course of the disease can span over decades especially if it is not treated.

Reference	Age of patient / year reported	Presentation	Treatment	Outcome	Comment
[29] Longcope W T. Sarcoidosis or Besnier-Boeck-Schaumann disease. Journal of the American Medical Association 1941; 117: 1321 - 1327	40 years 1941	Sudden death requiring post mortem	Not applicable	Not applicable	The first reported case from post mortem examination showing the sarcoidosis as part of systemic sarcoidosis
[30] Longcope and Fisher Longcope W T, Fisher A M. Involvement of the heart in Besnier-Boeck-	1942 40 years the same patient	Sudden death requiring post mortem	Not applicable	Not applicable	The first reported case from post mortem examination showing the sarcoidosis as part of systemic sarcoidosis

Schaumann disease Journal of the Mount Sinai Hospital 1942; 8: 784 - 797 reported a case of sarcoidosis which had affected the skin of a black man's penile shaft					(case reported twice)
[31] Carli G. Boeck-Schaumann of the balanoprepuical sulcus. Minerva Dermatol. 1955 Jun; 30(6): 178 – 180	28 years 1955	Painless 0.5 cm pink nodule on the balanoprepuical sulcus	Biopsy	Diagnosis was established by histological examination of biopsy specimen	Presence of multiple satellite sub-mucosal nodules and bilateral inguinal lymph node enlargement would suggest systemic sarcoidosis
[32] Vitenson J H, Wilson J M. Sarcoid of the glans penis J Urol. 1972 Aug; 108(2): 284 – 289	29 years when he was initially diagnosed as having sarcoidosis involving many organs but not penis; more than 34 years when he presented with penile lesion 1972	Painless mass growing on his glans penis for one and half years	Excision biopsy of the nodule	Diagnosis was established by histological examination	The fact that he had a number of sarcoidosis lesions elsewhere earlier would indicate that the sarcoidosis of the penis was part of systemic disease.
[33] Whittaker M, Anderson C K, Clark P B. Sarcoidosis of the penis treated by radiotherapy. Br. J. Urol. 1975 Jun; 47(3): 325 – 330	59 years 1975	Mild visible haematuria and dysuria et external urethral meatus	Biopsy of lesion on his penis	Diagnosis of sarcoidosis of penis was established by histological examination of specimen	The fact that a diagnosis of sarcoidosis affecting the submandibular gland was established 8 years earlier would indicate that the sarcoidosis of the penis was part of systemic sarcoidosis
[36] Rubinstein I, Baum G L, Hiss Y. Sarcoidosis of the penis: report of a case. J Urol. 1986 May; 135(5): 1016 – 1017	Age not available to author 1986	Chronic painful erythematous induration of the penis associated with many subcutaneous nodules and cutaneous ulcerations.	Application of topical steroids initially improved symptoms but this did not last long – biopsy of lesion	Diagnosis was established by histological examination of specimen	Knowledge that topical steroid treatment may initially be effective leading to improvement of the lesion but the lesion may relapse or progress further should be an indication for surgeons to make every effort to excise the lesions completely if it is possible.
[3] Mahmood N, Afzal N, Joyce A. Sarcoidosis of the penis. British Journal of Urology 1997; 80:155	67 years 1997	Urethral bleeding & dysuria & irregular haemorrhagic ulcerated lesion around the external urethral meatus.	Diagnosis was established by biopsy for histological examination	Diagnosis was established by histological examination of biopsy specimen Only transient improvement & lesion progressed Lesion progressed	The lesson learnt are that diagnosis earlier on of sarcoidosis elsewhere would indicate that the sarcoidosis of the penis was part of systemic sarcoidosis Complete excision of sarcoidosis penile lesion

			<p>Systemic steroids initially</p> <p>Meatal dilatation & Circumcisi on upon progress of lesion</p> <p>Partial amputation of penis upon further progress of lesion</p> <p>Radiothera py & chemother apy after further progress of lesion which was ineffective</p> <p>Total amputation of penis & perineal urethrosto my</p>	<p>Not effective on long term basis</p> <p>Not effective</p> <p>Total amputation of penis was effective</p>	<p>with normal surrounding tissue would appear to be the most effective treatment and there could progress or relapse of the lesion with steroid therapy only</p>
[37] Wei I, Friedman K A, Rudikoff D. Multiple Indurated papules on penis and scrotum. J Cutan Med Surg 2000 Oct; 4(4): 202 - 204	31 years 2000	lesions on his penile skin and scrotum which had been present for a period of two years interfering with sex life	Biopsy of lesion Details of treatment not available to author	Examination of biopsy specimen led to diagnosis Details of treatment & outcome not available	
[38] Rustscheff S. Sarcoidosis of the main reproductive organ Am J Respir Crit Care Med 189; 2014; A1541 URL: www.atsjournals.org online Abstracts Issue	57 years 2014	A growth on the shaft of penis in 2001	It was resected The lesion continued to progress and further biopsies were taken Biopsy of lesion in 2013	Histology showed non specific inflammation Diagnosis was not confirmed on histopathological examinations Diagnosis was confirmed by histology and he was put on prednisolone 20 mg daily	At times there may be difficulties in the diagnosis of sarcoidosis of the penis when other differential diagnoses may be considered initially as the diagnosis. In situations like this perhaps high levels of ACE and beta-2 microglobulin and low levels of 25-OH D3 in addition to presence of non-caseating granulomas would help establish the diagnosis of sarcoidosis. Within 6 weeks of being

					on prednisolone his penile lesion cleared in 2013 when treatment was given. This would illustrate that at times the use of steroid alone may lead to resolution of the lesion
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Conclusions

Even though sarcoidosis of the penis is uncommon, clinicians need to be aware that the disease exists and that sarcoidosis of the penis tends to be associated with variable presentations. A high index of suspicion is required with regard to the diagnosis of the disease. Clinicians who encounter the disease should be encouraged to report their cases so that the long term biological behaviour of the disease would be ascertained to enable establishment of consensus opinion on the management protocol that would enable preservation of the penis.

Conflict of Interest: None

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Desmos T C. Image of Sarcoidosis – Pathology www.meddean.luc.edu/lumen/MedEd/Radio/sarc/SARCPATH.html for making available figures from their site to be used and reproduced for non-commercial purposes.

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