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Journal of General Medicine and Clinical Practice

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Research Article

Sarcoidosis of Ovary, Fallopian Tubes, and the Uterus an Update

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Received date: December 03, 2024; Accepted date: December 21, 2024; Published date: January 24, 2025

Citation: Grey Venyo AK, (2025), Sarcoidosis of Ovary, Fallopian Tubes, And the Uterus an Update, *J. General Medicine and Clinical Practice,* 8(1); **DOI:10.31579/2639-4162/246**

Abstract

Sarcoidosis is stated to be a terminology that is used for a multi-system disease which is most commonly manifested within the pulmonary system. Nevertheless, cases of extrapulmonary manifestations of sarcoidosis had been sporadically reported frequently. Isolated occurrence of sarcoidosis within the uro-genital system is rare and has tended to pose a diagnostic and therapeutic dilemma. Uterine sarcoidosis could manifest with cervical erosions, endometrial polypoid lesions, and recurrent serometra. In majority of cases, it is diagnosed by endometrial curettage, but it had also been detected by examination of hysterectomy, polypectomy, and autopsy specimens. Cases of sarcoidosis of the ovary and sarcoidosis of the fallopian tube do manifest with symptoms and signs to simulate the manifestations of more common afflictions of the ovary and fallopian tubes. Non-necrotizing granulomas are the characteristic pathology examination finding of sarcoidosis. Nevertheless, many infectious and non-infectious etiologies including certain neoplasms could produce similar granulomatous reactions within the female genital tract. These conditions afflict the female genital tract more commonly than sarcoidosis, and therefore it is important to exclude these conditions first before making a diagnosis of sarcoidosis. Treatment of sarcoidosis is different from treating these other conditions and the most commonly utilized systemic or local corticosteroids could be hazardous if the underlying cause is infection. Sarcoidosis afflicting the ovary, fallopian tube and the uterus had not been extensively covered in most books of Medicine, obstetrics and gynecology and surgery perhaps due to the rarity of sarcoidosis in the aforementioned female genital organs when compared with the more common afflictions of the female genital tract. The ensuing chapter contains an updated information related to sarcoidosis including an overview and miscellaneous narrations from some case reports, case series, and studies related to sarcoidosis of the ovary, fallopian tube, and uterus.

Kew Words: sarcoidosis; ovary; fallopian tube; uterus; biopsy; histopathology; rare

Introduction

Sarcoidosis is a multisystem granulomatous disorder of unclear cause. [1] Sarcoidosis typically afflicts the lymph nodes of mediastinum, predominantly bilateral and/or pulmonary infiltrates. Extrapulmonary involvement of sarcoidosis had been documented in 30% to 50% of cases of sarcoidosis. Sarcoidosis of the female reproductive system is not common rare and sarcoidosis of the female genital tract is encountered in less than 1% cases of sarcoidosis. Sarcoidosis may afflict any organ, including: the vulva, the vagina, uterine cervix, the uterus, the fallopian tubes and ovary, and also the placenta and the breast of the female. The incidence of multiple localization of sarcoidosis on the female genitalia had been documented. In view of the rarity of sarcoidosis of the female genital tract, it would be envisaged that many clinicians including General Practitioners, gynaecologists, radiologists, pathologists, surgeons, paediatricians and other health care workers may not be familiar with the manifestations and diagnostic features of sarcoidosis of the ovary, fallopian tubes, and ovaries. Sarcoidosis of the female genital tract tends to proceed asymptomatically quite-often, and it has tended to be recognized only as an incidental finding. The diagnosis of sarcoidosis of the ovary, fallopian tubes and uterus is established based upon a thorough pathology examination of biopsy of the female genital organ lesion and details of the diagnostic features of sarcoidosis of the female genital tract can be ascertained in the overview aspect of the article.

Aim

To update the literature on sarcoidosis of the ovary, fallopian tubes and the ovary.

Method

Internet databases were searched including Google; Google Scholar; Yahoo; and PUBMED. The search words that were used included: Sarcoidosis of ovary; sarcoidosis of fallopian tubes; and sarcoidosis of the uterus. Eighty-four (84) references were identified which were used to write the article which has been divided into two parts: (A) Overview which has discussed general overview of sarcoidosis, and (B) miscellaneous narrations and discussions from some case reports, case series and studies related to

sarcoidosis of the ovary, sarcoidosis of the fallopian tubes and fewer narrations from sarcoidosis of the uterus.

Results

[A] **Overview**

Definition, General statements, Practice Essentials. [1]

- It has been iterated that Sarcoidosis is a multi-system inflammatory disease of unknown aetiology which predominantly afflicts the lungs and intrathoracic lymph nodes and is presented by the presence of non-caseating granulomas (NCGs) within afflicted organ tissues of the body. [1]
- It has been iterated that Sarcoidosis is typified by a seemingly exaggerated immune response against a difficult–to-discern antigen. [1] [2]
- The age-adjusted incidence of sarcoidosis is stated to be 11 cases per 100,000 population in whites but 34 cases per 100,000 population in African Americans. [1] [2]

Signs and symptoms

The presentation in sarcoidosis does vary depending upon the extent and severity of the organ that is involved as follows: [1]

- At times sarcoidosis may be asymptomatic, and incidentally detected upon chest radiograph images in about 5% of cases. [1]
- It has been stated that in 45% of cases, sarcoidosis may manifest with systemic complaints including fever, and anorexia, in 45% of cases. [1]
- It has been iterated that sarcoidosis in 50% of cases does manifest with pulmonary complaints including: dyspnoea on exertion, cough, chest pain, and haemoptysis on rare occasions. [1]
- It has been iterated that at times, sarcoidosis may manifest as neuro-sarcoidosis including: cranial neuropathies, leptomeningeal disease, intraparenchymal lesions, and myelitis, which does occur in between 5% to 10% of cases. [3]
- It has additionally been iterated that in sarcoidosis, Löfgren syndrome which manifests with fever, bilateral hilar lymphadenopathy, and poly-arthralgias does occur and this sarcoidosis affliction is common in Scandinavian patients, but uncommon in African-American and Japanese patients. [1]

The pulmonary findings on physical examination of patients afflicted by sarcoidosis had been summated as follows: [1]

- Usually there has tended to be normal pulmonary examination of patients afflicted with sarcoidosis. [1]
- In some cases of sarcoidosis, clinical respiratory tract examination of afflicted individuals may demonstrate audible crackles. [1]
- In some individuals afflicted by sarcoidosis, their clinical examination may demonstrate exertional oxygen desaturation. [1]

It has been iterated that dermatology presentations of sarcoidosis may include the ensuing: [1]

- Erythema nodosum. [1]
- A lower-extremity panniculitis with painful, erythematous nodules which often tend to be seen in association with Löfgren syndrome. [1]
- Lupus pernio, which is documented to be the most specific associated cutaneous lesion of sarcoidosis. [1]
- Violaceous rash upon the cheeks or nose tend to be common in cases of sarcoidosis. [1]
- Maculopapular plaques tend to be seen in some cases of sarcoidosis which has been stated to be an uncommon feature of sarcoidosis. [1]

It has been iterated that ocular involvement, in cases of sarcoidosis which may lead to blindness if untreated, may manifest as follows: [1]

- Anterior or posterior granulomatous uveitis, which is most frequently seen. [1]
- Conjunctival lesions as well as scleral plaques. [1]

Other possible manifestations of sarcoidosis to include the ensuing: [1]

- Osseous involvement. [1]
- Heart failure from cardiomyopathy may be encountered on rare occasions. [1]
- Heart block and sudden death of the sarcoidosis afflicted individual. [1]
- On rare occasions lymphocytic meningitis of the sarcoidosis afflicted individual. [1]
- On rare occasions, individuals who are afflicted by sarcoidosis may manifest with stroke, seizure, intracranial mass, hypopituitarism, neuropsychiatric symptoms, and encephalopathy and all these manifestations are stated to be rare. [1]

Diagnosis

The radiology-imaging studies for sarcoidosis had been summated as follows: [1]

- Chest radiography: It has been iterated that chest radiograph is central to the evaluation of sarcoidosis. [1]
- Routine chest computed tomography (CT): It has been iterated that the undertaking of computed tomography of the thorax adds little to radiography findings. [1]
- High-resolution CT (HRCT) scanning of the chest: It has been iterated that high-resolution CT (HRCT) scan may be helpful, in that it does identify active alveolitis versus fibrosis, and findings correlate with biopsy yield. [1]
- Gallium scans: It has been pointed out that Gallium scans are undertaken infrequently and that Gallium scan has a-low sensitivity and specificity, but may be helpful when the clinical picture remains confusing despite histology examination evidence of non-caseating granulomas, for example in differentiating chronic hypersensitivity pneumonitis from sarcoidosis. [1]

Staging of sarcoidosis has been summated as follows: [1]

- Stage 0: Normal chest radiographic findings
- Stage I: Bilateral hilar lymphadenopathy
- Stage II: Bilateral hilar lymphadenopathy and infiltrates
- Stage III: Infiltrates alone
- Stage IV: Fibrosis

It has been iterated that pulmonary function tests and a carbon monoxide diffusion capacity test of the lungs for carbon monoxide (DLCO) are used routinely in evaluation and follow-up of individuals afflicted by sarcoidosis. [1] and that some of the possible findings of the tests include the ensuing: [1]

- An isolated decrease in DLCO is the most common abnormality found in cases of sarcoidosis. [1]
- A restrictive pattern is seen in patients with more advanced pulmonary sarcoidosis disease. [1]
- About 15% to 20% of sarcoidosis patients are iterated to have obstruction. [1]
- It has been iterated that cardiopulmonary exercise testing is a sensitive test for the identification and quantification of the extent of pulmonary involvement. [1]
- Cardiopulmonary exercise testing also may indicate cardiac involvement that otherwise is not evident. [1]
- Impaired heart rate recovery during the first minute ensuing exercise had been demonstrated to be an independent predictor for cardiovascular and all-cause mortality, [4] and it might identify patients who are at high risk for the development of arrhythmias and sudden death.[5]
- It had been advised that all patients with sarcoidosis should have an annual electrocardiogram, and that patients who report palpitations should have a thorough evaluation with at least Holter monitoring.[1]
- Diagnosis of sarcoidosis requires biopsy in most cases. [1]
- Endobronchial biopsy via bronchoscopy is often undertaken. [1] The yield is stated to be high; and it has been iterated that results of the biopsy may be positive even in patients with normal chest radiographs. [1] The central histopathology examination finding is the presence of non-caseating granulomas with special stains negative for fungus and mycobacteria. [1]

Routine laboratory evaluation is stated to be often unrevealing, but possible abnormalities include the following: [1]

- Hypercalcemia (about 10-13% of patients)
- Hypercalciuria (about a third of patients)
- Elevated alkaline phosphatase level
- Elevated angiotensin-converting enzyme (ACE) levels.

Management

The management of sarcoidosis has been summated as follows: [1]

It has been iterated that non-steroidal anti-inflammatory drugs (NSAIDs) are indicated for the treatment of arthralgias and other rheumatic complaints. [1] It has also been stated that patients with stage I sarcoidosis often do require only occasional treatment with NSAIDs. [1]

Treatment in sarcoidosis patients with pulmonary involvement has been summated as follows:

- Asymptomatic patients may not require treatment at all and would need to be observed.
- In sarcoidosis patients with minimal symptoms, serial re-evaluation is important. [1]
- Treatment is indicated for sarcoidosis patients with significant respiratory symptoms. [1]
- Corticosteroids can produce small improvements in the functional vital capacity and in the radiographic appearance in sarcoidosis patients with more severe stage II and III disease. [1]

For extrapulmonary sarcoidosis involving such critical organs such as the heart, liver, eyes, kidneys, or central nervous system, corticosteroid therapy is stated to be indicated. [1] It has been iterated that topical corticosteroids are effective for ocular disease. [1] For pulmonary sarcoidosis disease, it has been iterated that prednisone is generally given daily and then tapered over a 6-month course. It has also been stated that high-dose inhaled corticosteroids could be an option, particularly in sarcoidosis patients with endobronchial disease.

Common indications for non-corticosteroid agents in cases of sarcoidosis had been stated to include the ensuing: [1]

- Steroid-resistant disease
- Intolerable adverse effects of steroids
- Patient desire not to take corticosteroids

Non-corticosteroid agents that tend to be used in sarcoidosis include the ensuing: [1]

- Methotrexate (MTX) had been a successful alternative to prednisone. [1]
- Chloroquine and hydroxychloroquine had been used for cutaneous lesions, hypercalcemia, neurologic sarcoidosis, and bone lesions. [1]
- Chloroquine had been found to be effective for acute and maintenance treatment of chronic pulmonary sarcoidosis. [6] [7]
- Cyclophosphamide had been rarely used with modest success as a steroid-sparing treatment in patients with refractory sarcoidosis. [8] [9]
- It has been iterated that Azathioprine is best used as a steroid-sparing agent. [1] [10]
- It has been stated that Chlorambucil might be beneficial in patients with progressive disease unresponsive to corticosteroids or when corticosteroids are contraindicated. [1] [11]
- It had been iterated that cyclosporine might be of limited benefit in skin sarcoidosis or in progressive sarcoid resistant to conventional therapy. [1] [12]
- It has been iterated that Infliximab, [13] [14] and thalidomide, [15] [16] had been used for refractory sarcoidosis, particularly for cutaneous disease, as well as for the long-term management of extrapulmonary sarcoidosis. [17]

- It had furthermore, ben iterated that Infliximab appeared to be an effective treatment for patients with systemic manifestations such as lupus pernio, uveitis, hepatic sarcoidosis, and neuro-sarcoidosis. [1]

It had also been iterated that for sarcoidosis patients with advanced pulmonary fibrosis from sarcoidosis, lung transplantation remains the only hope for long-term survival and that indications for transplantation include either or both of the following. [18]:

- Forced vital capacity below 50% predicted [1]
- Forced expiratory volume in 1 second below 40% predicted. [1]

[B] Miscellaneous Narrations and Discussions from Some Case Reports, Case Series, And Studies Related to Sarcoidosis of The Ovary and Fallopian Tubes.

Wuntakal, et al. [19] reported a 40-year-old para four obese Caucasian woman who had a two-year history of lower abdominal pain and who was referred from a peripheral hospital for the further management of bilateral adnexal masses. She had computerised tomography (CT) scan of abdomen and pelvis which had shown a complex cystic lesion of 7cm to 8 cm within her right adnexum and bilateral ureteric obstruction. All of her baseline blood tests including haematology and tumour markers (CA 125 -26 IU/ml) were reported to be normal. The results of her serum tests had shown normal liver function and moderately impaired renal function (creatinine 10–15, urea > 200). She had a complex medical history which included: obstructive sleep apnoea, asthma, glaucoma, hypothyroidism, hypertensive cardiomyopathy and bipolar disorder; she was registered disabled. She also had a copper intra uterine contraceptive device in situ over the preceding three years. Given her body habitus (BMI 42), her abdominal and pelvic examination was difficult and non-specific. The only finding of relevance that was noted was bilateral adnexal fullness. She was managed within the gynaecological oncology multi-disciplinary framework (MDT). On reviewing her CT scan films, the features that were noted included: bilateral basal pleural thickening, bilateral hydronephrosis, retroperitoneal lymphadenopathy associated with retroperitoneal fibrosis as well as bilateral adnexal cystic masses. There was a small volume of ascites. She had magnetic resonance imaging (MRI) which was undertaken for further characterisation of the adnexal masses. The right adnexal complex cystic lesion was noted to have measured 8 cm × 7 cm × 7 cm in diameter and had a thick wall of up to 2 cm, which was noted to be irregular. There were several septations, some of which measured 3 cm to 4 mm. There were no enhancing papillary formations, although the wall and septa enhanced. The appearance suggested an ovarian lesion with possible involvement of the fallopian tube. The left adnexal cyst measured 5 cm × 6 cm × 4 cm, had a smooth wall and contained a single thin septation, which was consistent with a benign ovarian cyst. Both cysts contained fluid, which was low on T1 and high on T2, with no evidence of fat or blood. Encompassing the cysts posteriorly, the fat was noted to be streaky in appearance and there was marked thickening of the adjacent fascial planes, with thickening of the meso- rectal fascia up to 1 cm. The fascial thickening extended up the pre-sacral space and along the posterior aspect of the pelvic sidewalls, resulting in the obstruction of the ureters. Enlarged lymph nodes that measured up to 1.8 cm in short axis, were present along both pelvic sidewalls, which were striking due to the very high T2 signal intensity (see figure 1). Nodes were also visualised within the inguinal and para-aortic regions. Even though the imaging appearances could not exclude an ovarian neoplasm, the features noted above were adjudged to be suggestive of an inflammatory process. In view of the woman's medical history and clinical status the MDT recommendation was clinical review and radiology-imaging guided biopsy of lymph nodes for pathology examination.

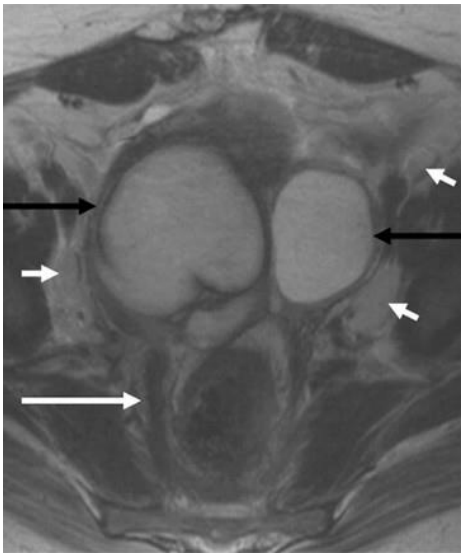


Figure 1

MRI axial T2W images of the pelvis. Bilateral adnexal cystic masses are demonstrated (black arrows). The cyst wall on the right side is thick and irregular. There is marked thickening of the meso-rectal fascia (long white arrow). Multiple prominent nodes are demonstrated along the pelvic sidewalls, which are very high in signal intensity on T2W (short white arrows). Reproduced from [19] under the Creative Commons Attribution License.

She underwent CT guided right inter iliac node biopsy, following an unyielding biopsy of inguinal nodes. Histopathology examination of the biopsy specimens demonstrated non-caseating granulomatous lymphadenitis with negative stains for acid-fast bacilli and fungi. There was no foreign body visualised. Given the histopathology examination findings the attention of the authors was directed towards an inflammatory process. She was subsequently referred to respiratory physicians, with a working diagnosis of sarcoidosis. She was also referred to urologists for the management of retroperitoneal fibrosis and bilateral hydronephrosis. Her abdominal pain prompted insertion of bilateral JJ ureteric stents. The physicians, commenced a (step-down) course of prednisolone. Symptomatic improvement was found

but the renal function did not change. Her repeat radiology imaging demonstrated resolution of hydronephrosis. The woman was reviewed again clinically following the course of steroids. During this interval the physicians had ordered an autoantibody screen as autoimmune disease could co-exist with sarcoidosis; the screen was negative (Rheumatoid factor, anti-DNA antibody and antinuclear antibody). Upon her examination there was no evidence of any palpable lymphadenopathy observed. An ultra sonographic examination six months subsequently demonstrated a bulky uterus and reduction in the size of the right adnexal cyst. Repeat radiology imaging (MRI axial T2W image) a further two months subsequently demonstrated resolution of the left adnexal cyst. There was a small residual cyst upon the right and marked decrease in the thickening of the meso-rectal fascia. The lymph nodes appeared to be normal (see figure 2). The retroperitoneal fibrosis upon imaging had resolved. Her CA125 remained normal. At the time of publication of the article, the patient was under joint care between the respiratory and renal physicians with symptomatic improvement.

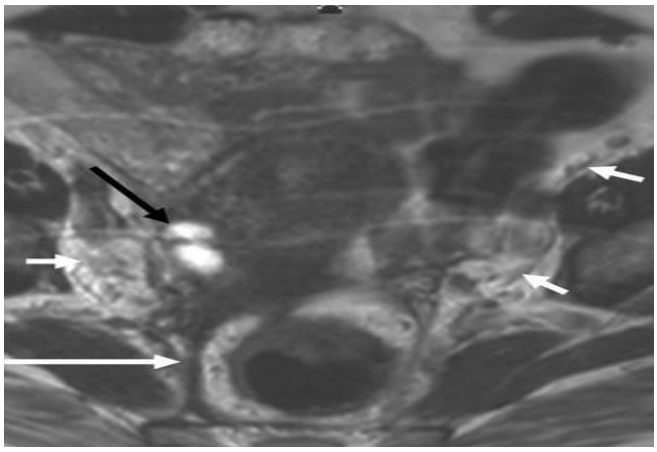


Figure 2

MRI axial T2W image of the pelvis following treatment for sarcoidosis. The left adnexal cyst has resolved. There is a small residual cyst on the right (black arrow). There is marked decrease in the thickening of the meso-rectal fascia (white arrow). The lymph nodes appear normal (short white arrows). Reproduced from [19] under the Creative Commons Attribution License. Wuntakal, et al. [19] made the ensuing educative discussions:

- Boeck in Norway first identified sarcoidosis over 100 years ago and Sarcoidosis was originally called Boeck's disease. Sarcoidosis was defined in 1960 as a systemic granulomatous disease of undetermined aetiology and pathogenesis [20].
- Sarcoidosis has high prevalence in European countries (Sweden and Denmark).
- The UK prevalence rate of sarcoidosis is 20 per 100 000, and the incidence is iterated to increase from north to south. [21]
- The primary targets of sarcoidosis include the ensuing: the lungs, lymph nodes, liver and spleen. Ovarian sarcoidosis presenting as bilateral adnexal masses is extremely rare whether as a component of systemic disorder or as an isolated finding. [22]
- Both the presentation and the findings in cases of sarcoidosis could mislead a clinician towards sinister diagnosis.
- The aetiology of sarcoidosis has remained not clear.
- The onset of sarcoidosis has been iterated to be most common between the ages of 20 years and 40 years of age and sarcoidosis usually manifests with bilateral hilar lymphadenopathy and pulmonary infiltration.
- Clinical presentations such as: amenorrhoea, menorrhagia, post-menopausal bleeding and erosion of the cervix had also been reported. [21]
- Upon the basis of histology and clinical as well as radiological response of the woman to first line anti-sarcoid treatment, the case they had reported had fulfilled the criteria for the diagnosis of sarcoidosis.
- Only a few cases of sarcoidosis of the female genital tract had been reported in the literature, and Winslow et al [23] felt this may be due to under reporting of the true incidence.
- The most common site of sarcoidosis affliction of the female reproductive system is the uterus.
- Ovarian sarcoidosis is an extremely rare condition and is known to simulate ovarian malignancy. Up to the time of publication of their case in 2007, only seven cases of ovarian involvement had been reported in the English language literature. [22] [23] [24] [25] [26] [27] [28]. Four of these cases had demonstrated uterine involvement as well on pathological examination.
- Their reported case was the first case with a non-surgical approach in a patient with ovarian sarcoidosis.
- In the reported cases up to 2007, the age of the patients had ranged between 32 years and 72 years.
- The gynaecological problems in these women were post-menopausal bleeding, menorrhagia, cervical carcinoma in situ, abdominal pain and abdominal distension. Three of the seven patients did not have any previous history of documented sarcoidosis and it was an incidental finding in the remaining cases.
- In their reported case, the main presenting complaint was abdominal pain with adnexal masses leading to cancer referral.
- Preoperatively in one case, the CT scan of the abdomen had demonstrated enlarged lymph nodes within the para-aortic and mesenteric region and in the second case the mediastinal nodes were enlarged [22] [24]

- Clinically and radiologically an ultrasound scan and CT scan a mass was identified within the pelvis in three cases prior to surgical treatment [22] [24] [28]
- In their reported case the retroperitoneal nodes were also enlarged.
- In three reported cases, the women underwent exploratory laparotomy with a provisional diagnosis of ovarian malignancy but the histopathology examination diagnosis was sarcoidosis. The CA-125 was between 248–477 IU/ml [22] [24] [25].
- Postmenopausal bleeding, menorrhagia and cervical carcinoma in situ accounted for the other four women who had undergone hysterectomy and bilateral salpigo- oophorectomy. The pathology examination of the specimen suggested sarcoidosis. [23] [26] [27] [28]
- More obscure causes of the genital tract granulomas include the ensuing: coccidiomycosis, lymphogranuloma inguinale, foreign body reaction and leprosy. Bacteriological proof is essential to differentiate these lesions from sarcoidosis. These can be differentiated by the undertaking of appropriate history taking, special staining of tissues and microscopic findings. [24] [28]
- There are no specific radiology-image findings in the literature to describe ovarian sarcoidosis.
- In the opinion of the radiologists, an intra-abdominal, and thoracic, inflammatory process rather than malignancy was more likely to explain the findings.
- The striking feature on the MRI of their reported woman was the presence of marked thickening of fascial planes, which is not typical of ovarian cancer. The serum CA 125 level was raised in 80% of epithelial ovarian cancer. Given the normal level of CA 125 and unusual radiology-image findings it reassured them that this was not obviously an ovarian malignancy.
- Following the undertaking of a CT guided lymph node biopsy an empirical diagnosis of sarcoidosis was made upon the basis of clinical and laboratory findings with histological support. The woman was managed conservatively, given the woman's poor anaesthetic profile. A percutaneous biopsy of her lymph node facilitated arrival at the diagnosis with minimal morbidity.
- Even though White et al [22] had reported the coexistence of mucinous cystadenoma of the ovary and ovarian sarcoidosis. In their case given the resolution of pelvic mass with steroids it was unlikely to be cystadenoma.
- Their subsequent clinical review and repeat radiology-imaging pursuant to steroid therapy had demonstrated resolution of the left adnexal cyst. The lymph node biopsy together with follow-up radiology-imaging post treatment had offered evidence to indicate that the process was likely to be sarcoidosis. Given the clinical and radiology-image improvement of the patient, following MDT discussion the woman was satisfactorily discharged from their care to be monitored by physicians.
- Their reported case in point did not only illustrate a rare manifestation of sarcoidosis affecting the ovary but had also highlighted the importance of managing such complex women in a MDT environment to optimise care.
- MDT approach could function as an ideal conduit for the management of complex patients with complex adnexal masses.
- The presence of an expert diagnostic radiologist in this setting is important for the determination of the subsequent modality of care.
- Even though pre-operative radiology-imaging of adnexal masses is routine but where doubt exists regarding the diagnosis, a simple pre-operative radiology-imaging guided biopsy of suitable tissue could help avoid the undertaking of major surgery and the attending risks.
- The resources of the MDT had ensured appropriate care and optimum outcome for their reported woman.

Wuntakal, et al. [19] made the ensuing conclusions:

- They had described a case of ovarian sarcoidosis, which is a rare clinical entity.
- The manifestation could simulate the manifestation of carcinoma. Therefore, optimum management of such patients should be delivered within a multi-disciplinary team (MDT) environment.

Marak et al. [29] made the ensuing iterations:

- Sarcoidosis is a multisystem disease of unclear aetiology.
- Any organ system within the body can be afflicted by sarcoidosis, and the classic pathology examination finding is the presence of non-caseating granulomas within the involved organs.
- Pulmonary sarcoidosis is the most common presentation of the disease, accounting for 90 percent of the cases. [30]
- It has been iterated that extra pulmonary sarcoidosis is also common, with skin, eyes, liver, and reticuloendothelial manifestations accounting for the majority of the cases of between 10% to 25%.
- The involvement of other organ systems such as cardiovascular, nervous system, upper respiratory tract, renal, spleen, thyroid, gastrointestinal tract, musculoskeletal, and exocrine glands accounts for only a minority of cases of between 0.4% and 5%.: [30] [31] [32] [33]
- Most of the cases of sarcoidosis with extra pulmonary sarcoidosis have coexisting pulmonary disease. This was demonstrated by ACCESS research group where 368/736 which accounted for 52% of their patients had concomitant pulmonary involvement and only 14 out of 736 which amounted to 1.9% of their patients had isolated extra pulmonary sarcoidosis. [34].
- Involvement of the female reproductive system by sarcoidosis is very rare.
- Unlike other extra pulmonary manifestations, there is not much data available for this variant of sarcoidosis; whatever little information is available is mostly based upon case reports.

Marak et al. [29] reported a 45-year-old African American premenopausal female, gravida 1 and para 1, chronic active smoker (20 pack years), and with a past medical history significant for schizophrenia and chronic obstructive pulmonary disease, who presented to their facility with menorrhagia. She had recently been treated for latent syphilis with penicillin, and she also had

genital warts and herpes virus 2 infections. Three years preceding her manifestation, she had presented with mediastinal adenopathy and thick-walled pulmonary cavities which had both of her upper lobes. Flexible bronchoscopy with bronchoalveolar lavage and transbronchial biopsies obtained from the right upper lobe had on pathology examination demonstrated non-necrotizing granulomas which were consistent with sarcoidosis. They were negative for AFB and fungal stains. A diagnosis of primary cavitary pulmonary sarcoidosis was made, and she was treated with systemic steroids for twelve months. She responded well to steroids with complete clinical and radiology image features of resolutions (see figures 3 (a) and 3 (b)). Fourteen months earlier, she had presented with epigastric and right upper quadrant pain of a one-month duration. She underwent esophagogastroduodenoscopy which demonstrated a clean gastric ulcer along the lesser curvature and a markedly erythematous and oedematous antrum. Pathology examination of biopsy specimens from the gastric antrum demonstrated features of chronic gastritis and non-necrotizing granulomas which was adjudged to be consistent with her previous diagnosis of sarcoidosis. Her symptoms resolved with proton pump inhibitors, and she did not require additional therapy with steroids for her gastric sarcoidosis. During her current admission, she had manifested with menorrhagia of two-month duration. At her baseline, her menstrual cycles had been regular and lasted for 3 days to 4 days. Her vitals and systemic examinations were unremarkable. Her pelvic examination demonstrated multiple sub-centimetre white ulcerated lesions which had involved her labia majora. Her hemoglobin level was 9.5 gm/dL and the rest of her routine laboratory workup including complete blood count, coagulation profile, liver, and renal function tests was normal. She tested negative for HIV. She had chest roentgenogram, which did not demonstrate any abnormality. On transvaginal ultrasound scan, the size of her uterus was found to measure 12.1 × 6.5 × 8.2 cm^3 with an endometrial thickness of 6 mm. It also demonstrated an anterior body mural fibroid with a submucosal component that measured 4.3 × 3.7 × 4.4 cm^3 and a fundal fibroid that measured 2.9 × 2.7 × 2.9 cm^3; her ovaries were normal. She received a short course of high dose oral contraceptive pills. Pathology examination of punch biopsies from the vulvar lesions demonstrated high grade squamous intraepithelial lesions with features of human papillomavirus infection. Therapeutic endometrial curettage was undertaken, and the histopathology examination of the endometrial tissues demonstrated menstrual phase changes, strands of smooth muscles suggestive of uterine myoma, and numerous non-necrotizing epithelioid giant cell granulomas (see figures 2 (a) and 2 (b)). Stains and cultures for bacteria, fungal, and mycobacteria were negative, and she was diagnosed as having uterine sarcoidosis. She had been amenorrhoeic and asymptomatic since she underwent a therapeutic endometrial curettage.

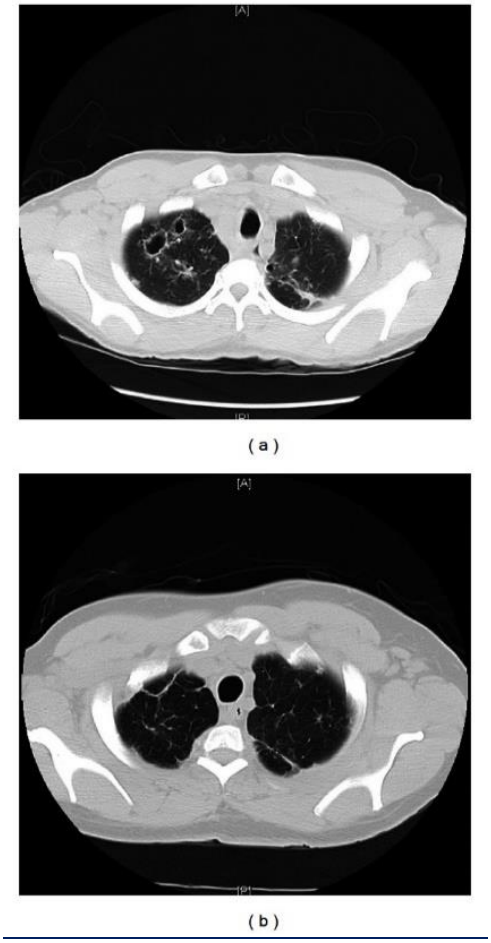
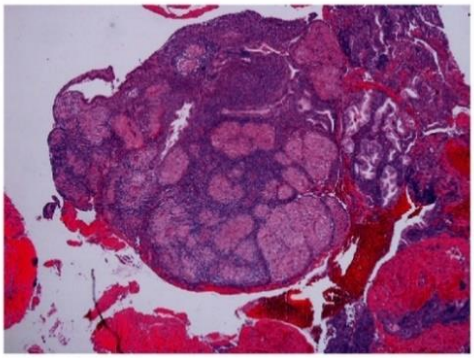
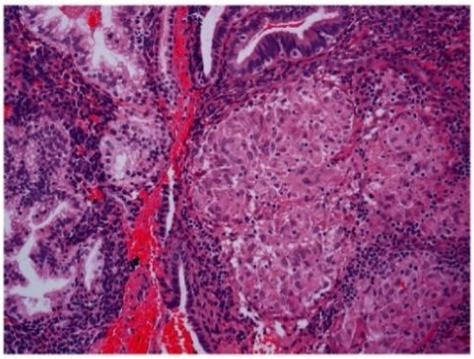


Figure 3:(a) CT scan of chest revealing cavitary lesions. (b) CT scan of chest shows resolution of cavitary lesions. Reproduced from: [29] under the Creative Commons Attribution License.



(a)



(b)

Figure 4: (a) Hematoxylin and eosin (H&E) stain at low magnification shows noncaseating granulomas. (b) H&E stain at high magnification shows a follicular pattern of granulomas, asteroid bodies, and the absence of necrosis. Reproduced from: [29] under the Creative Commons Attribution License.

Marak et al. [29] made the ensuing educative discussions:

- Sarcoidosis of the female genital tract is probably the rarest form of all the extra pulmonary sarcoidosis, accounting for less than 1% of cases. [37].
- Based upon their literature review, it seemed that the uterus is the most commonly afflicted organ of the female genital tract. [19] [36]
- In 1933, Garland and Thompson first described an autopsy finding of sarcoidosis which had involved the uterus in a 28-year-old female. Since its first description in 1933 till 1988, only 21 cases of female genital tract sarcoidosis had been reported in the literature. [35].
- In the ensuing years, there had been just a few more reported cases of uterine sarcoidosis [37 - 46].
- The majority of the cases occur in the reproductive age of between 21 years and 40 years, even though a case of uterine sarcoidosis in a 64-year-old postmenopausal woman had also been described. [47].
- Like any other extra pulmonary manifestation of sarcoidosis, the majority of the patients had concomitant pulmonary involvement and the disease seems to occur more frequently in the Black population.
- A majority of the patients had manifested with menstrual irregularities; menorrhagia, metrorrhagia, and postmenopausal bleeding are more commonly reported symptoms than amenorrhea. [35] [36] [37] [38] [39] [40] [41] [42] [43] [44] [45].
- Some of the patients were asymptomatic, and the diagnosis was established based upon examination of the hysterectomy or autopsy specimens. [35].
- Some cases of uterine sarcoidosis had manifested with cervical erosions. [36], endometrial polypoid lesions, [46] and recurrent serometra. [44].
- Others were incidental findings upon cervical pap smear [45] and patients who underwent surgery for uterine myomas.
- Endometrial curettage had enabled the diagnosis in the majority of the cases; in others the diagnosis was made upon examination of the hysterectomy, polypectomy, and autopsy specimens. [35] [45] [46]
- Sampling bias probably does account for the increased reporting of uterine sarcoidosis compared to other parts of the female genital tract. [36].
- Cases of uterine sarcoidosis with concomitant involvement of the ovaries and fallopian tubes had also been reported. [35] [47].
- Isolated cases of uterine sarcoidosis are usually self-limiting and have good prognosis; there appears to be no detrimental effect on pregnancy outcomes despite the presence of granulomas in the placenta. A majority of the patients do not require treatment and can be monitored; nevertheless, systemic steroids may be helpful in symptomatic patients. [36].
- Ovarian sarcoidosis is probably the second most common presentation of female genital tract sarcoidosis.
- Winslow and Funkhouser in 1968 described a case of a 28-year-old female who underwent total abdominal hysterectomy with bilateral salpingoophorectomy for a cervical lesion. [48] Histopathological examination demonstrated sarcoid-like

lesions involving the uterus, right fallopian tube, and the right ovary. Since then, there had been other reports of ovarian involvement by sarcoidosis. Like uterine sarcoidosis, most of the reported cases occurred in the reproductive age group. [19] [48] [49] [50] [51] [52] [53], although a few cases of ovarian sarcoidosis in postmenopausal women have also been reported. [54] [55] [56]. Symptoms can be nonspecific, such as fever, malaise, and abdominal pain, [57], or they can present with clinical features concerning for ovarian tumours, such as ovarian enlargement, weight loss, obstructive uropathy, intraperitoneal mass, and ascites associated with thickening of the omentum and peritoneal nodular deposits. [19] [49] [50] [51] [52] [56].

- In these cases, diagnosis was made based upon histopathological findings and excluding other causes of granulomatous inflammation. Some of these patients had elevated CA-125 levels, which are typically elevated in patients with ovarian tumours and carcinoma of the female genital tract. [50] [51] [52]. CA 125 is elevated also in various non-gynaecology malignancies and other benign conditions as well. [52]. CA 125 elevation is probably from increased production by epithelioid cells present in the granulomas or is due to increased production by peritoneal cells in response to inflammatory mediators secreted by sarcoid granulomas. [52]. There have been reports of ovarian tumours with sarcoid-like lesions involving the bone marrow and regional lymph nodes. [57] [58] [59]. These sarcoid-like reactions occur in other malignancies, such as lymphomas, breast cancer, primary lung cancer, renal cell, and gastric cancers. Usually, these reactions are limited in distribution mostly involving the regional lymph nodes, but multiorgan involvement consistent with systemic sarcoidosis can develop simultaneously or following chemotherapy. [57] [58] [59] [60] [61] [62] [63] Finding a sarcoid-like lesion calls for careful examination for other adjacent lesions that may be masking malignancy. This is probably due to dysregulation in the Th1/Th2 immunity in these situations, and sarcoidosis in itself has been shown to have enhancement of the Th1 immunity. [64] [65] Careful examination of the pathology specimens is therefore indicated as these granulomatous lesions can easily be confused with metastatic disease and can cause treatment dilemma. Most of these patients tend to be symptomatic and have a good response to steroids with resolution of enlarged ovaries, intrapelvic mass, ascites, and normalization of CA 125 levels. [19] [50] [51] [52] [56].
- Involvement of the fallopian tubes commonly occurs in conjunction with sarcoidosis of the other parts of female genital tract. In 1954, Cowdell described an autopsy finding of sarcoidosis involving the fallopian tubes of a 21-year-old female who died of cardiac sarcoidosis. [35] [66]
- Subsequently more cases of tubal sarcoidosis have been described but the diagnosis was made mostly on pathologic examination of salpingectomy specimens in patients who were being treated for other gynaecological problems. Most of these patients had menstrual irregularities, some had fibroids, [35] and one of the patients had dyspareunia and infertility. [66]
- At the time of surgery distension of the tubes, pelvic adhesions and miliary deposits of sarcoid granulomas may be seen involving the tubes, uterus, ovaries, ligaments, omentum, and intestines. [19] [49] [50] [66]. Vaginal sarcoidosis is the rarest of all, and only two cases have been reported up to the time of publication of their article. [67] [68].
- One of the cases had pulmonary sarcoidosis who had presented with vaginal itching and irritation and responded to systemic and topical steroids. Vulval sarcoidosis is another rare manifestation of sarcoidosis with only five cases reported up to the time of publication of their article. [69] [70] [71] [72] [73]. One of the patients had manifested with papular rash involving the labia majora and the perineum; the second one presented with a painful nodular lesion at the site of the previous episiotomy site, and the third one presented with vulvar mass. Two of the patients had pulmonary sarcoidosis. Details on the other two were not available.
- Non-necrotizing granulomas are the characteristic pathologic finding of sarcoidosis. Nevertheless, this finding is not pathognomonic of sarcoidosis and many infectious and non-infectious aetiologies including: certain neoplasms could produce similar granulomatous reactions in the female genital tract.
- Infectious aetiologies include tuberculosis, atypical mycobacteria, endemic mycosis, actinomycosis, and parasites.
- Non-infectious causes like foreign body reaction, Crohn's disease, medications, lymphoma, and other neoplastic conditions and post-procedure or postsurgical granulomas can also mimic sarcoid granulomas. [74] [75] [76].
- These conditions afflict the female genital tract more commonly than sarcoidosis, and therefore it is important to exclude these conditions first before prematurely making a diagnosis of sarcoidosis.
- Treatment of sarcoidosis is different from treating these other conditions and the most commonly used systemic or local corticosteroids can be hazardous if the underlying cause is infection.

Marak et al. [29] made the ensuing conclusions:

- Female genital tract sarcoidosis is rare and its presentation can simulate other conditions which commonly afflict the female genital tract.
- Diagnosis of sarcoidosis is mainly based upon the identification of non-caseating granulomas within the involved organs and excluding other conditions that can have a similar histopathology finding.
- Sarcoidosis can affect any age group but usually occurs in the reproductive age group.
- Like other extra pulmonary manifestations of sarcoidosis, the majority of the patients have pulmonary involvement and the Black population seems to be afflicted more frequently than other races.
- Increased incidence of uterine sarcoidosis may just reflect a sampling bias as most of these cases had concomitant involvement of other structures of the female genital tract.
- Endometrial curettage or even pap smear might be sufficient to make the diagnosis of uterine sarcoidosis; involvement of other structures will need a biopsy.
- Isolated cases of sarcoidosis may just require observation but systemic and symptomatic patients may be given a trial of systemic steroids.

Turkay et al. [77] made the ensuing iterations:

- Sarcoidosis is stated to be a chronic multi-system disorder of unknown aetiology, which is characterized, histologically, by the presence of non-caseating epithelioid granulomas.
- The sarcoidosis disease could afflict every organ system; nevertheless, ovarian involvement is extremely rare.
- According to Wuntakal et al, seven cases of ovarian involvement had been reported in the English language literature by 2007 [19].
- Ovarian sarcoidosis might be misdiagnosed by radiologists as a solid ovarian malignancy.
- They had reported a case of ovarian mass which, despite the presence of radiology imaging features suggestive of an ovarian malignancy, had demonstrated a significant decrease in size over a relatively short period of time, a phenomenon that is more consistent with ovarian sarcoidosis.

Turkay et al. [77] reported a 50-year-old Caucasian woman who had a history of abdominal discomfort and pain for three months who was referred from an outside hospital. She had needed a recommendation for further management of a unilateral, complex, solid-mass lesion that measured 9 cm × 6.5 cm × 5 cm within her left adnexum and for multiple enlarged lymph nodes which were found upon abdominal ultrasonography (US). She had a medical history of right salpingo-oopherectomy, and her case was managed within the gynaecology/oncology multidisciplinary framework. She had an MRI scan which demonstrated a left adnexal mass accompanied by a complex cyst (see figure 5). Multiple enlarged lymph nodes were demonstrated within her paraaortic, left common and internal iliac (see figure 5), and inguinal regions, that measured up to 2.5cm on the short axis.

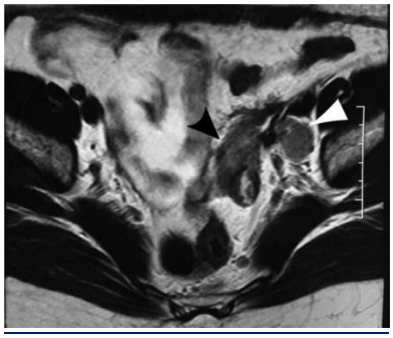


Figure 5

50-year-old woman with ovarian sarcoidosis. T2-weighted MR image of the pelvis depicting left adnexal mass (black arrowhead) concomitant with posteriorly localized complex cystic lesion and enlarged lymph node (white arrowhead) in the left internal iliac chain. Reproduced from [77] Under the Creative Commons Attribution License.

PET/CT revealed a left adnexal mass with increased FDG uptake (SUD max=5.2) (see figure 6). Multiple left iliac, para-aortic, and inguinal enlarged lymph nodes (SUD max=6.2) were noted, along with mediastinal, hilar, and bilateral supraclavicular enlarged lymph nodes (SUD max=7.9 in the mediastinum) (see figure 7). In light of these findings and the patient's clinical picture, the gynaecological/oncologic multidisciplinary team recommended clinical review and imaging-guided lymph-node biopsy.

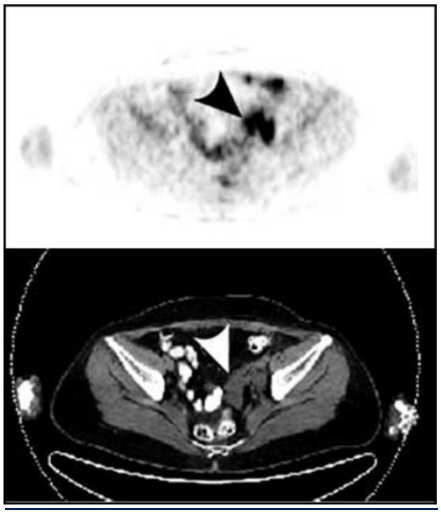


Figure 6:

50-year-old woman with ovarian sarcoidosis. PET/CT scan depicts a left adnexal mass (arrowheads) with left internal iliac lymph nodes, both demonstrating increased FDG uptake. Reproduced from [77] Under the Creative Commons Attribution License.

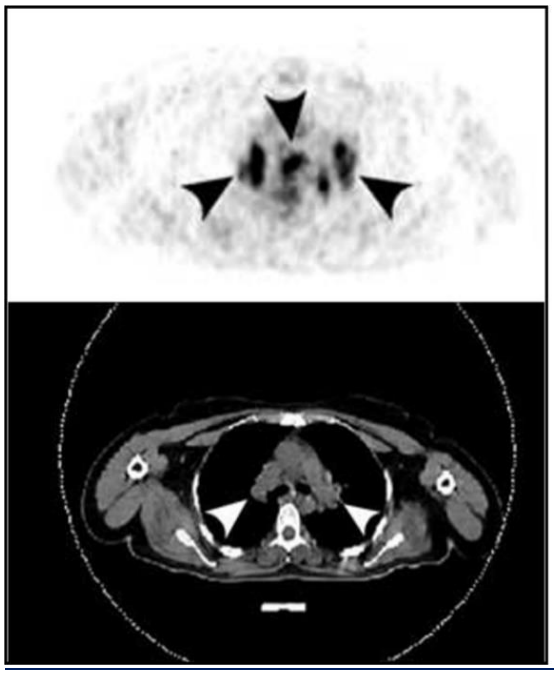


Figure 7:

50-year-old woman with ovarian sarcoidosis. PET/CT scan demonstrates bilateral hilar and subcarinal enlarged lymph nodes (arrowheads) with increased FDG uptake. Reproduced from [77] Under the Creative Commons Attribution License.

After a two-month period of evaluation and multidisciplinary care, the decision was made to perform an ultrasound to determine the most appropriate lymph node to biopsy for further evaluation. A subsequent decrease in ovarian mass size over this two-month period prompted further imaging with MRI. This revealed marked regression of the mass to 4x3x2.5cm; however, the previously present lymph nodes persisted on exam (see figure 8). There was no interval progression or development of new lymph-node involvement. The woman underwent US-guided right internal iliac lymph-node biopsy, following a non-differentiating biopsy of inguinal nodes. Histology revealed noncaseating granulomatous lymphadenitis with negative stains for acid-fast bacilli and fungi. No foreign body was seen. Given the histological findings, our attention was then directed to an inflammatory process. With a working diagnosis of sarcoidosis, the patient was subsequently referred to a pulmonologist who performed bronchoscopy with bronchoalveolar lavage, bronchial biopsy, transbronchial biopsy, and mediastinal lymph-node biopsy. A transbronchial right-lower-lobe biopsy revealed noncaseating granulomatous inflammation, and lymph-node biopsy revealed epithelioid histiocytes with noncaseating granulomatous inflammation (see figure 9). Based on these clinical, radiological, and histologic findings, we arrived at the extremely rare diagnosis of sarcoidosis.

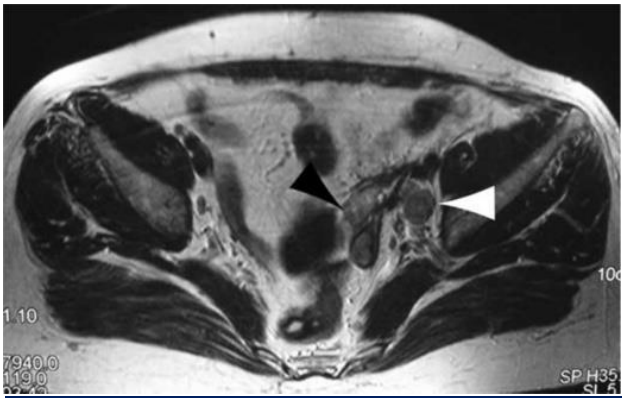


Figure 8:

50-year-old woman with ovarian sarcoidosis. T2-weighted axial pelvic MRI depicts regression of the left adnexal mass (black arrowhead) despite persistence of the left internal iliac lymph node (white arrowhead) with the complex cystic lesion. Reproduced from [77] Under the Creative Commons Attribution License.

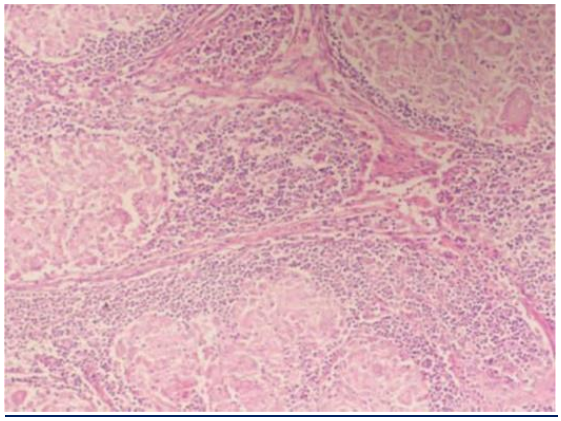


Figure 9:

50-year-old woman with ovarian sarcoidosis. 50-year-old woman with ovarian sarcoidosis. Non-necrotizing granuloma with epithelioid histiocytes artery (x100) Reproduced from [77] Under the Creative Commons Attribution License.

Turkay et al. [77] made the ensuing educative discussions:

- Sarcoidosis has a variety of clinical and radiologic manifesting features.
- Sarcoidosis commonly afflicts young and middle-aged adults, and frequently manifests with bilateral hilar lymphadenopathy, which is the most common radiology image finding and may occur with associated pulmonary infiltrates, and ocular and skin lesions [78].
- Other organs might also be involved.
- Genitourinary tract sarcoidosis is observed in 5% of patients in autopsy series [78].
- Kidney manifestations of sarcoidosis are interstitial nephritis, glomerulonephritis, and nephrocalcinosis due to hypercalcemia [78] [79].
- Kidney functions are usually protected, and radiology imaging is possible. In such cases, contrast-enhanced CT scan depicted striated nephrograms [78] [79].
- The epididymis is the most affected organ in genital sarcoidosis, followed by testicular involvement (which is very rare and particularly accompanied by the epididymis) [21] [78] [79].
- Acute epididymo-orchitis or painless masses within the scrotum and testicular swelling could be clinical manifestations [21].
- Characteristically, testicular involvement of sarcoidosis is multiple and bilateral [78] [79].
- Ultrasound scan (US) depicts multiple hypoechoic nodules which demonstrate low signal intensity on T2-weighted MRI and show enhancement after contrast injection [78].
- Sarcoidosis of the female genital tract is extremely rare, with the most common site of involvement being the uterus [21] [78].
- One of the major concerns of female genital sarcoidosis is its differentiation from other lesions like tuberculosis. Amenorrhoea, menorrhagia, metrorrhagia, and postmenopausal menorrhagia are clinical manifestations of female genital sarcoidosis [21].
- Cervix and fallopian involvement are also reported [21].
- Cases of reported ovarian sarcoidosis are even rarer [19].
- The unusual clinical manifestation of the disease, and the radiology-imaging features simulating ovarian malignancies, present a problem in the differential diagnosis for an ovarian mass.
- A majority of the cases of ovarian sarcoidosis were diagnosed after laparoscopy [19] [22].
- Their reported case was one of the few cases of ovarian sarcoidosis that was diagnosed via a nonsurgical approach.
- Sarcoidosis spontaneously remits in up to 33% of patients [80].
- During the period of evaluation, they had been able to recognize the specific regression of the adnexal mass over time; this had caused them to reconsider their differential diagnosis of the patient's ovarian mass.
- Spontaneous regression of solid ovarian malignancies is stated to be a rare [81] [82] and extremely unexpected situation.
- As far as they were aware, among differential diagnosis of solid ovarian malignancies, spontaneous regression is limited only to germinal ovarian tumours in the reported English literature [81] [82]. Regression of ovarian masses might be a distinctive feature, and clinicians may use it to evaluate ovarian masses in the future.
- Up to the time of publication of their article, no specific radiological findings had best described the occurrence of ovarian sarcoidosis, nor are there any nuclear medicine findings specific to the diagnosis.
- FDG uptake in sarcoidosis, for example, is non-specific in both intensity and pattern. In fact, the FDG uptake pattern of ovarian sarcoidosis can simulate other processes, including that of (but not limited to) ovarian malignancy, diffuse metastatic disease, and lymphoma [79] [80].
- Given that sarcoidosis frequently afflicts many organ systems, familiarity with the radiology and clinical features of the disease in various organs could play a crucial role in its diagnosis and management for patients afflicted with the disease.
- While ovarian sarcoidosis is rarely reported in the literature, they had speculated that ovarian sarcoidosis may be more common than clinicians think, especially in the diagnostic workup of patients with ovarian masses.
- They would like to remind clinicians that, in the differential diagnosis of solid ovarian masses, sarcoidosis should be considered despite its reported rarity within the published literature.

Kuno et al. [83] stated the following:

- Sarcoidosis is a systemic granulomatous disease which is most commonly manifested within the pulmonary system.
- Even though the entire aetiology of sarcoidosis had remained not known, it had been reported that Propionibacterium acnes (P. acnes) had been isolated from sarcoid lesions.

Kuno et al. [83] reported a case of salpingitis which had arisen from sarcoidosis. Kuno et al. [83] reported a female patient, who was aged 37 years, gravida 2 para 0, and who had been diagnosed with sarcoidosis at the age of 36 years. She underwent laparoscopic right salpingectomy due to obvious right hydrosalpinx with recurrent refractory right lower abdominal pain. The pathological examination diagnosis was granulomatous salpingitis of the right fallopian tube suspecting sarcoidosis. Immunocytochemistry using a specific monoclonal antibody against P. acnes lipoteichoic acid (PAB antibody) demonstrated PAB-positive reaction in sarcoid granuloma. Kuno et al. [83] concluded that their reported case was the first case of sarcoidosis in which the presence of P. acnes was shown in sarcoid lesions within the fallopian tube.

Boakye et al. [84] stated the ensuing:

- Female reproductive tract sarcoidosis is a rare clinical condition, especially when the fallopian tube is the site of involvement.
- Their search of the medical literature revealed in 1997, 22 cases of female genital tract sarcoidosis, with 6 cases involving the fallopian tube.

Boakye et al. [84] reported a case of sarcoidosis of the genital tract which occurred in a woman with a 16-year history of pulmonary sarcoidosis. Boakye et al. [84] concluded that:

- Since various diseases, including sarcoidosis and tuberculosis, cause similar histopathology changes, obtaining bacteriological proof is mandatory, for the diagnosis could have therapeutic and public health implications

Conclusions

- Taking into consideration knowledge of the fact that sarcoidosis frequently afflicts many organ systems, familiarity with the radiology-image and clinical features of sarcoidosis within various organs could play a pivotal role in its early diagnosis and prompt and appropriate management for patients who are afflicted by sarcoidosis.
- While sarcoidosis of the ovary and sarcoidosis of fallopian tubes are rarely reported in the literature, there is the possibility that sarcoidosis of the ovary as well as sarcoidosis of the fallopian tubes may be more common than had been reported in the literature and perhaps if in the diagnostic workup of patients with ovarian masses and symptoms of salpingitis are thoroughly assessed with radiology image-guided biopsies for pathology examination, more cases of sarcoidosis of the ovary and fallopian tubes would be diagnosed.
- Similarly, if lesions of the uterus including provisionally diagnosed uterine fibroids and other lesions are subjected to radiology image guided biopsies for pathology examinations, perhaps more cases of sarcoidosis of the uterus would be diagnosed by pathologists.
- All clinicians globally should be aware that in the differential diagnosis of abnormal uterine masses, solid ovarian masses, salpingitis and pelvic inflammatory disease (PID) they should consider sarcoidosis as a differential diagnosis despite the reported rarity of sarcoidosis of the ovary, fallopian tubes and the uterus within the published literature.

Conflict Of Interest

Acknowledgements

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DOI:10.31579/2639-4162/246