RS3PE and Benign Endometriotic Cyst in a Young Lady

Ewe Jin Koh[1], Shu Hui Ng[1] and Ee Ling Lai[1,2*]

[1]Department of Internal Medicine, Hospital Sultan Ismail Johor Bahru, Perak, Malaysia

[2]Department of Internal Medicine, Hospital Taiping, Perak, Malaysia

Corresponding Author*

Ee Ling Lai

Department of Internal Medicine,

Hospital Sultan Ismail Johor Bahru,

Perak, Malaysia

E-mail: lai.eeling@yahoo.com

Received date: November 27, 2020**; Accepted date:** December 16, 2020**; Published date:** December 23, 2020

Abstract

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is an uncommon disease and occurs more frequently in older adults. It is characterized by symmetrical distal synovitis, pitting edema of the hands and feet, with negative Rheumatoid Factor (RF) and anti-cyclic citrullinated peptide (anti-CCP). An association with rheumatological diseases, malignancies-either solid organ tumor or hematological malignancies - and benign conditions are well-reported. We describe a young lady who was diagnosed with RS3PE, and who had an incidental finding of benign left ovarian endometriotic cyst. She responded well to a short course of low dose prednisolone with no recurrence of symptoms after surgical removal of the ovarian endometriotic cyst, suggestive of a possible association of RS3PE and benign gynaecological tumour.

Keywords: RS3PE; Endometriosis; VEGF

Background

In 1985, McCarty et al first described a case series of remitting symmetrical seronegative synovitis with pitting edema in 23 patients. It was initially thought to represent an entity of Rheumatoid Arthritis spectrum (RA) [1]. However, the lack of bony erosions, negative RF, and anti-CCP has made RS3PE a distinct disease by itself. It is a rare rheumatological disease and typically affects elderly males, with symmetrical synovitis and pitting edema of hands and feet characterizing this disease. Although the exact pathogenesis remains unknown, elevated serum Vascular Endothelial Growth Factor (VEGF) has been proposed as the possible causative factor [2]. VEGF is a potent angiogenic factor, up-regulated in many tumors, and its role in tumor angiogenesis is well established [3]. In relation to this, both hematological and solid organ tumors have been reported in RS3PE [4,5]. Furthermore, RS3PE can occur in association with autoimmune diseases and benign conditions [6-9]. So far, there is a paucity of evidence demonstrating a distinct relationship between RS3PE and benign endometriotic cysts. This case report describes a case of RS3PE in a young lady with benign left ovarian endometriotic cyst.

Case Presentation

Miss SA* is a 34-year old single, nulliparous lady who presented with episodic painless swelling of both hands for the past 5 years. It was not associated with joint pain or stiffness, skin color changes, or limitation in range of movement. In addition, she also noticed intermittent episodes of bilateral pedal edema extending until the mid-shins. These episodes subsided spontaneously within days. She denied heart failure symptoms such as angina, orthopnea, or paroxysmal nocturnal dyspnea. Apart from that, there was no urinary symptom for example frothy urine. She has no neck swelling or hypothyroid symptoms like cold intolerance, weight gain or constipation. Her menses were regular with no complaints of dysmenorrhea or menorrhagia. She has no respiratory or abdominal symptoms. There were no constitutional symptoms such as prolonged fever, loss of appetite, or loss of weight. There was no positive family history of malignancy or connective tissue disease (Figure 1).

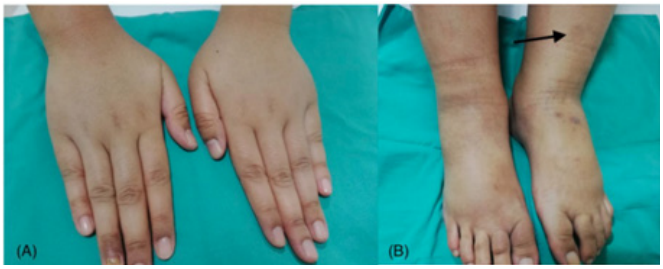

Figure 1. (A) Photo showing the bilateral hands edema extending until the wrists level. (B) Photo showing pitting edema (arrow) of the bilateral feet.

Our clinical examination revealed symmetrical swelling of both hands extending proximally until the forearms, and bilateral pitting edema until the mid-shin level. The overlying skin was neither erythematous nor warm. There was no joint tenderness elicited. There was also no neck swelling. Jugular Venous Pressure (JVP) was not raised (Figures 2 and 3).

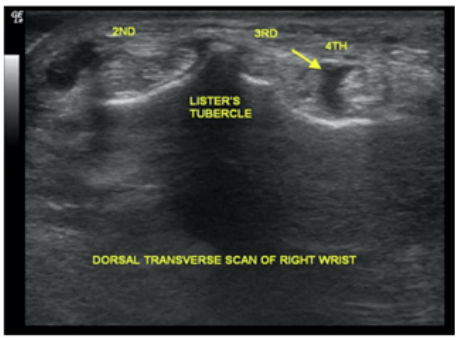

Figure 2. Dorsal transverse scan of right wrist reveals tenosynovitis of the fourth extensor compartment tendons (arrow).

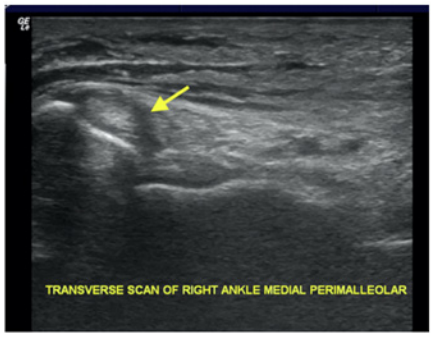

Figure 3. Transverse scan of right ankle medial perimalleolar demonstrated tenosynovitis of the posterior tibialis tendon (arrow).

On examination of her abdomen, a 26-week size pelvic mass was palpable, which was firm to hard in consistency. Otherwise, no hepatosplenomegaly or lymphadenopathy was detected. Breast examination was normal. Cardiovascular and respiratory examinations were both normal, with normal vesicular breath sounds and no crepitation indicative of fluid overload. Neurological examinations were unremarkable (Figure 4).

Investigations

Blood investigations revealed iron deficiency anemia, with a hemoglobin level of 10.8 g/dL and a total iron level of 2.9 mcmol/L. ESR was raised at 52 mm/hour, but a normal CRP at <40 mg/L. Renal and liver profiles were unremarkable. There was no evidence of proteinuria on urinalysis. Her chest radiograph was also normal with no features of cardiomegaly. Thyroid function test was normal, ruling out hypothyroidism (TSH: 3.49 mU/L, free T4: 16.9 pmol/L). Further investigations revealed negative anti-nuclear antibody (ANA), Rheumatoid Factor (RF), and anti-Cyclic Citrullinated Peptide (anti-CCP).

Radiographic examination of the hands and feet was normal with no evidence of bony erosions. Further point-of-care sonographic assessment of both hands and feet revealed subcutaneous edema with tenosynovitis of the extensor tendons of bilateral wrists and tendons of bilateral tibialis anterior, peroneal and extensor digitorum.

Additional workup was performed to search for underlying associated malignancy. Her Ca-125 level was marginally raised at 44 U/mL (reference range 0-35 U/mL). Other tumor markers were within the normal range i.e. alpha fetoprotein <1.3 ng/mL (reference range 0-8 ng/mL), Carcinoembryonic Antigen (CEA) 1.6 ng/ml (reference range 0-5 ng/mL), and beta-human chorionic gonadotrophin (βHCG)<2.0 IU/L (reference range 0-2 IU/L). The full blood picture was not suggestive of a hematological malignancy. Computed tomography of the thorax, abdomen, and pelvis revealed a large, well-circumscribed, thin-walled cystic mass arising from the left adnexa extending into the lower abdomen, measuring 25 cm × 15 cm × 22 cm, likely left ovarian in origin, with mass effect causing bilateral hydroureter and hydronephrosis. There was no lymphadenopathy or evidence of distant metastasis.

Treatment

She was commenced on oral prednisolone 10 mg once daily for 2 weeks with subsequent complete resolution of the edema of bilateral hands. However, the lower limb edema improved only partially and decision was made to prolong the treatment duration. Oral prednisolone 10 mg once daily was tapered off in one month and the lower limb edema eventually subsided. She underwent a laparotomy to remove the huge left ovarian mass within one month of her RS3PE diagnosis and steroid therapy initiation. Post-operative histopathological examination of the left ovarian mass revealed a benign endometriotic cyst.

Outcome and follow up

The patient recovered from her surgery uneventfully. After surgical resection of the left ovarian endometriotic cyst, her symptoms of episodic swelling of the bilateral hands and feet never recurred. The inflammatory markers reduced, with the latest ESR of 32 mm/Hr (reference range<20 mm/Hr). Her hemoglobin level normalized to 12.3 g/dL. She did not require recommencement of prednisolone, and there was no recurrence of RS3PE. Currently, she is still being followed up in our rheumatology clinic with no new complaints.

Results and Discussion

When remitting symmetrical seronegative synovitis with pitting edema (RS3PE) was first introduced by McCarty et al in 1985, it was thought to be a subset of rheumatoid arthritis [1]. However, it is now felt to be an entity distinct from RA based on a constellation of features, namely a negative rheumatoid factor, the lack of radiographic bony erosions, good corticosteroid responsiveness, and excellent prognosis without the need for Disease-Modifying Anti-Rheumatic Drugs (DMARDs) [10]. RS3PE is characterized by symmetrical synovitis and pitting edema of the hands and feet. In recent years, with the introduction of musculoskeletal ultrasound, tenosynovitis of the extensor and/or flexor tendons of wrist and extensor tendons of the feet have been identified as an additional defining feature of RS3PE [11].

It is an uncommon disease with an incidence rate of 0.09% in the Japanese population [12], and is said to occur more frequently in older adult males. RS3PE can occur by itself without underlying disease, or can develop in association with other disorders. Malignancies - both solid tumors or hematological in nature - have been reported in association with RS3PE [4,5]. The average malignancy rate was estimated at about 20% based on the pooled data from European, American, and Asian patients with RS3PE [13]. RS3PE may precede or follow the diagnosis of an underlying malignancy, hence lending credence to the postulation that RS3PE may be a paraneoplastic manifestation of a malignancy. Other than that, RS3PE also occurs in patients with other rheumatological diseases such as systemic lupus erythematosus [6] and Sjogren's syndrome [7]. RS3PE also has been reported in benign conditions, for example, diabetes mellitus [8], insulin therapy [9], and infection [14].

Although the exact underlying pathophysiology of RS3PE remains unknown, studies have suggested that raised serum vascular endothelial growth factor (VEGF) plays a vital role [2]. Data from study by Arima et al suggests that serum VEGF in RS3PE patients was markedly increased compared to the control group [2]. VEGF has also been shown to be a potent angiogeneic factor VEGF, causing vasodilation and increasing vascular permeability, which leads to hypervascularity and subsequent synovitis and subcutaneous edema. The decrease of VEGF in RS3PE after glucocorticoid treatment further highlights the role of VEGF in RS3PE [15].

Endometriosis commonly affects women at a reproductive age. It is characterized by the presence of ectopic endometrium tissue outside of the uterus. Colonization of the ovary surface inclusion or a functional follicular cyst by the ectopic endometrium tissue leads to the formation of ovarian endometriotic cyst. In endometriosis, angiogenesis is increased and vascular endothelial growth factor (VEGF), a potent angiogenesis factor, appeared to play an important role [16,17]. Studies have shown that VEGF is increased significantly in peritoneal fluid of patients with endometriosis and in ovarian endometrioma [18]. Although there have been no reported case of RS3PE in endometriosis to date, both conditions reliably demonstrate raised VEGF levels. Therefore, we postulate that an elevated VEGF level due to endometriosis may be associated with the RS3PE syndrome in this patient. Unfortunately, serum VEGF assay was not available in our institution, making objective correlation of these two conditions difficult.

One peculiar phenomenon in our patient was the episodic appearance of the RS3PE which resolved spontaneously after a few days. In a study by McLaren et al, there was a cyclical variation of VEGF concentration, where the VEGF concentration in the proliferative phase is significantly higher than the secretory phase of the menstrual cycle [18]. Hence, we postulate that the fluctuation of serum VEGF concentration during menstrual cycle may lead to the episodic occurrence of RS3PE in this case.

Corticosteroid is the mainstay of therapy for RS3PE. Patients with idiopathic or related benign conditions with RS3PE often show an excellent response to low dose steroids (prednisolone <15 mg) and are able to withdraw therapy eventually. Conversely, patients with concomitant neoplasia often respond poorly to steroids, and treatment of the underlying malignancy is needed. Our patient, who had benign ovarian endometriotic cyst responded well to a short course of low dose prednisolone and did not experience recurrence of the RS3PE syndrome after surgical removal of the ovarian endometriotic cyst.

Conclusion

To our best knowledge, this is the first reported case of RS3PEwith plausible association with ovarian endometriotic cyst. The proposed underlying mechanism is likely due to elevated VEGF levels in endometriosis that leads to RS3PE. Further studies needs to be carried out to investigate the correlation between serum VEGF in endometriosis and the occurrence of RS3PE.

Conflict of Interest

None declared.

Contributions

EJ Koh and EL Lai diagnosed and managed the patient. SH Ng, EJ Koh and EL Lai contributed equally to the conception, drafting and revision of this case report. All authors approved the final manuscript.

Acknowledgment

There was no specific funding for this case report. We would like to thank the patient for consenting to the write up of this case report.

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Cite this article: Lai EL (2020) Rs3pe and benign endometriotic cyst in a young lady. Med Rep Case Stud 6: 1.