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Research Article

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Incidental Leukocytoclastic Vasculitis in the Context of IV Methamphetamine Use Following Syncope

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Abstract

A Caucasian female in her early fifties presented to the authors' emergency department for assessment following an unconscious collapse post IV methamphetamine use. On examination an incidental finding of a vasculitic rash on the patient's legs resulted in investigations and a likely diagnosis of Primary Sjogren's Syndrome (PSS). Punch biopsy revealed a leukocytoclastic vasculitis, which can be the presenting feature of pSS. Serology results that supported the diagnosis were exceptionally high RF titre extremely high RF titre (482 IU), ANA speckled pattern (1:2560), positive anti Ro/SSA and anti LA/SSB antibodies and hyperglobulinaemia. Notably the patient had a history of recurrent nephrolithiasis which is also commonly seen in association with pSS. This case demonstrates the importance of recognising rheumatic diseases that contribute to emergency department presentations as well as the usefulness of opportunistic biopsy and screening in such patients. Particularly in rural emergency department settings this can assist diagnosis and treatment in settings where rheumatology services are lacking.

1. Introduction

A Caucasian female in her early fifties presented to the authors' emergency department by ambulance in the early hours of the morning following an unconscious collapse at home. This occurred following intravenous IV methamphetamine use in the late part of the evening. By the time the patient arrived in the emergency department she was complaining of right sided facial numbness, but otherwise felt well.

The patient reported using methamphetamine in the form of ice once, or twice a week to provide her with sufficient energy to complete household chores. The patient stated she experienced significant fatigue impacting her ability to perform activities of daily living and that ice was a way of managing the situation. The patient had a long-standing history of IV drug use spanning over 2 decades. She reported using heroin in the past.

The patient's past medical history included nephrolithiasis requiring lithotripsy. She reported previous thyroid problems, but could not elaborate further. The patient was not on any regular medications and had no known drug allergies. On examination, the patient appeared well and comfortable as a slightly overweight middle-aged female. Her vital signs were within normal parameters and she was afebrile.

The patient had a normal neurological examination with the exception of objective and subjective sensory changes, reporting numbness of her face bilaterally and numbness of her lower limbs bilaterally from the mid-calf to the feet. No other objective focal neurological findings were elicited during assessment with normal power, tone, reflexes and coordination.

Heart sounds were dual with no murmurs. A respiratory examination was unremarkable.

The patient's abdominal examination was normal with no signs of hepatosplenomegaly. No lymphadenopathy was noted.

On examination of the lower limbs, the patient was noted to have a wide spread bilateral rash extending from the knees, distally to the toes. The rash was non blanching with palpable purpura (see Figure 1). The patient reported the rash was intermittent, and it had been present for at least 12 months. When she had visited her GP to discuss it, the rash had resolved. An injection site was noted distal to the knee and medially on the right leg. The patient reported symptoms around her ankles of pain and a burning

sensation, however there was no overt synovitis, or joint effusion on examination of the patient's ankles, or joints of the feet.

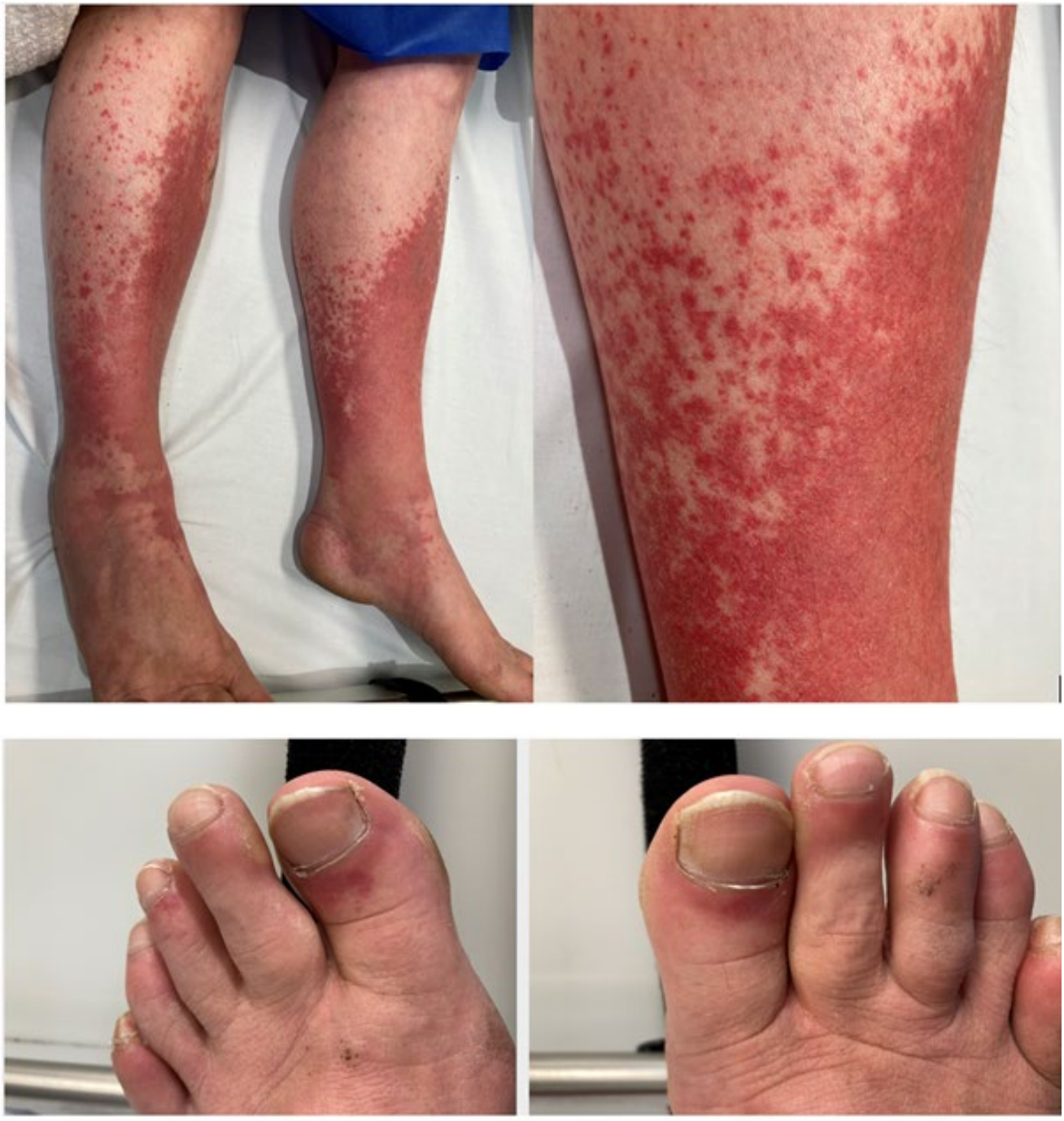

Figure 1.0 Bilateral Non-Blanching Purpuric Rash

Two 5mm skin biopsies were performed on the patient's right lateral anterior lower leg and were sent for histology and immunofluorescence.

Investigations included serology, chest X-ray, ECG, CT brain.

2. Results:

A CT brain did not reveal any acute intracranial pathology.
A chest X ray did not demonstrate any acute changes.
An ECG was unremarkable.

Full Blood Count			
Serological Marker	**Level**	**Units**	**Reference Range**
Haemoglobin	130	g/L	135-175
White cell count	7.99	x10*9/L	4.0-11.0
Platelet count	267	x10*9/L	150-450
Red cell count	4.88	x10*12/L	4.50 -6.00
Haematocrit	0.41	L/L	0.40-0.50
Mean Cell volume	83.4	pg	27-33
Mean platelet volume	9.6	fL	80-98
Vasculitis Serology			
Serological Marker	**Level**	**Units**	**Reference Range**
ANA	Positive 1:2560 speckled pattern		
ENA	Positive SSA/Ro60 Antibody positive SSA/Ro52 Antibody positive All other ENA antibodies negative		
Lupus anticoagulant	Negative		
Anticardiolipin antibody	Negative		
Beta-2-glycoprotein	Negative		
HBV	Negative		
HCV	Negative		
Ds-DNA	Negative		
ANCA	Negative		
Rheumatoid Factor	**482**	**IU/mL**	**<=15**
Complement C3	1.35	g/L	0.90-1.8
Complement C4	0.14	g/L	0.10-0.4
Multiple Blood Analysis			
Serological Marker	**Level**	**Units**	**Reference Range**
Sodium	135	mmol/L	135-145
Potassium	3.6	mmol/L	3.5-5.2
Chloride	100	mmol/L	95-110
Bi carb	28	mmol/L	22-32
Anion gap	15	mmol/L	7-17
Urea	7.0	mmol/L	3.2-5.5
Creatinine	88	mmol/L	2.7-8.0
eGFR	67	mmol/L	60-110
Calcium level	2.90	umol/L	>=60
Ionised calcium level	1.37	mL/min/1.73m2	2.10-2.60
Phosphate	1.09	mmol/L	0.75-1.50
Magnesium	0.83	mmol/L	0.7-1.10
Albumin	44	mmol/L	34-48

Globulin	**48**	**g/L**	**21-41**
Total protein level	**92**	**g/L**	**60-80**
Bilirubin	13	umol/L	2-24
GGT	14	U/L	30-110
ALP	109	U/L	0-55
AST	46	U/L	0-45
LDH	218	U/L	120-150
CRP	18.8	Mg/L	0.0-8.0

Table 1: Serology Results

As there was no emergent cause identified for the patient's presentation to emergency department, she was considered safe to be discharged from the emergency department with advice to follow up with her GP, to review the vasculitis serology.

Histology results of the skin biopsy were reported the following week revealing perivascular inflammation composed of neutrophils, histocytes and lymphocytes. Neutrophilic debris was noted around blood vessels as well as within the interstitium. Fibrinoid necrosis was demonstrated. Extravagated red blood cells were present. The features were consistent with leukocytoclastic vasculitis with no fungal organisms identified on specimen stains.

Once the histology results were received, the patient was discussed by phone with the nearest rheumatology centre located at a tertiary hospital. It was decided not to commence the patient on prednisolone as she did not demonstrate respiratory, cerebral, or renal involvement. She was referred for rheumatology review for 2 weeks from the phone call with the advice she should return to the emergency department to complete HIV testing, cryoglobulin testing and ESR.

The patient was contacted twice by phone, once requesting her to return to emergency department to complete additional tests, however despite these phone calls, the patient was lost to follow up and failed to attend subsequent rheumatology review.

3. Discussion:

Following is a discussion on why Primary Sjogren's Syndrome (pSS) is the most likely diagnosis in this presentation with the following differential diagnoses considered:

- Sarcoidosis
- Systemic Lupus Erythematosus
- Drug-induced leukocytoclastic vasculitis (methamphetamine-related)
- Infective leukocytoclastic vasculitis

Features of the patient's presentation that make Primary Sjogren's Syndrome more likely over other diagnoses are the following features:

- Patient age
- Extremely high RF titre (482 IU)
- ANA speckled pattern (1:2560)
- Positive anti Ro/SSA and anti LA/SSB antibodies
- Hyperglobulinaemia
- Patient's reported disabling fatigue
- Symmetric ankle arthralgia with bilateral ankle pain
- Peripheral bilateral lower limb objective and subject numbness
- Complaint of chronic intermittent oral and ocular dryness

These last two symptoms reported by the patient were discovered only on questioning in a phone call follow up 2 weeks after the patient's initial presentation and not at the time of initial assessment.

Primary Sjogren's Syndrome (pSS) is a relatively common autoimmune disease. Prevalence varies globally depending on patient demographics, but is reported to occur in rup to 2% of the adult population with only 50% of cases appropriately diagnosed [1]. pSS has a pooled prevalence rate of 60.82 cases per 100,000 patients according to and a female predominance of 9:1, as is typical of many autoimmune rheumatic diseases. pSS typically affects middle-aged and older females.

Several features favouring a diagnosis of primary Sjogren's Syndrome will now be discussed.

Extremely high RF titres, positive ANA, Anti Ro/SSA and anti LA/SSB antibodies and hyperglobulinaemia have all been reported in pSS [2], with Anti Ro/SSA antibodies being the most specific serologic marker [3, 4]. This patient's ENA was positive for both SSA antibodies and the RF titre was very high at 482IU/mL.

The high RF with positive speckled pattern ANA is in keeping with pSS. Many pSS patients are incorrectly diagnosed with RF as a result of this common serological finding [5]. High RF titres should be correlated with the clinical presentation and other serology to avoid this diagnostic error occurring. A symmetrical non-erosive oligoarthritis is the most common pattern of joint involvement in pSS and ankles are the most frequently involved joint, followed by shoulders and wrists [6, 7]. This patient reported chronic bilateral ankle pain without signs of synovitis on examination.

Neurological involvement in pSS is common and presents in 20-70% of cases often preceding sicca symptoms by 2 years [6]. The patient's reported long standing bilateral lower limb numbness possibly represents a peripheral sensory neuropathy that is in keeping with this common feature of pSS. Peripheral numbness can also be a feature of vasculitis in pSS and is reported in 31% of patients with pSS as vasculitis in one case study by Scofield [8].

Vasculitis is a recognised feature of pSS, with 10% - 58% of patients who develop vasculitis presenting with cutaneous lesions according to Scofield [9]. Cutaneous manifestations of pSS are present in 16% to 50% of cases. Cutaneous vasculitis is associated with anti-Ro (SSA) positive patients who are RF positive [10, 11]. A range of cutaneous and systemic vasculitdes are reported in the literature in association with pSS.

Debilitating fatigue occurs in 70% of patients with pSS which was one of the patient's primary complaints and the reason she was reportedly self-medicating with methamphetamine [12]. Baer [13] suggests a diagnosis of Primary Sjogren's Syndrome can be made on the basis of oral dryness, anti Ro and anti La antibodies and positive rheumatoid factor, however to meet the more strict 2016 ACR/EULAR classification criteria for Primary Sjogren's Syndrome (see Table 2) the patient should undergo objective testing including:

Measurements for ocular dryness:

- Positive surface staining (using lissamine green and, or rose Bengal staining)
- Abnormal Shirmer testing<5 mm/5 minute

Evidence of salivary gland dysfunction:

- Abnormal biopsy findings suggestive of acute, or chronic sialadenitis
- Abnormal sialometry
- Abnormal salivary gland ultrasound findings [14]

The classification of SS applies to any individual who meets the inclusion criteria*, does not have any condition listed as exclusion criteria**, and who has a score ≥ 4 when summing the weights from the following items:	
Item	**Weight / Score**
Labial salivary gland with focal lymphocytic sialadenitis and focus score ≥ 1.	3
Anti-SSA (Ro) +	3
Ocular staining score ≥ 5 (or van Bijsterfeld score ≥ 4) on at least one eye4	1
Schirmer ≤ 5 mm/5min on at least one eye	1
Unstimulated whole saliva flow rate ≤ 0.1 ml/min5	1
* The patient must have symptoms of ocular, or oral dryness lasting longer than 3 months which can include a sensation of gritty eyes and, or requiring liquids to assist with swallowing dry foods **The following conditions must be excluded in making a diagnosis of pSS: • History of head and neck radiation treatment • Active Hepatitis C infection (with positive PCR) • Acquired Immunodeficiency Syndrome • Sarcoidosis • Amyloidosis • Graft Versus Host Disease • IgG4-related disease	

Table 2. ACR-EULAR Classification Criteria for primary Sjögren's syndrome (pSS)

Authors note the failure to perform cryoglobulin testing at the time of initial assessment. Cryoglobulins can play a role in leukocytoclastic vasculitis and are elevated in 10.6% of patients with 6.5% presenting with cryoglobulinemic vasculitis that can be life-threatening according to [15]. Cryoglobulins were unfortunately omitted from the initial serology work up.

Whilst hypercalcemia is common in pSS the exact prevalence of hypercalcemia in pSS is not known. The patient's elevated calcium was long standing and might have played a contributory role in the patient's development of nephrolithiasis.

Nephrolithiasis in pSS is the result of distal renal tubular acidosis (dRTA) which produces hypercalciuria and hypocitraturia [16, 17]. Although dRTA in pSS has been long recognised [18] the exact mechanism by which pSS leads to dRTA remains unknown. The patient had a history of recurrent renal calculi with long standing elevated calcium noted at the time of her presentation to ED. Nephrolithiasis occurs in 14-32% of patients with pSS [16] [19]. Elevated serum calcium is one of the many abnormal markers occuring in pSS and has been recognised as attributing to renal dysfunction [19, 20].

pSS with comorbid sarcoidosis and secondary SS can occur in the context of sarcoidosis [21, 22, 23, 24]. The presence of granulomas is suggestive of the presence of sarcoidosis, rather

than pSS. This patient had a normal ALP making sarcoidosis a less likely diagnosis. Of note, exclusion of sarcoidosis is required for a diagnosis of pSS, however given the number of case reports in the literature of concomitant disease the relationship between these 2 diseases represents an area requiring further research and evaluation.

pSS has been reported in association with immune dysregulation resulting in destruction of the parathyroid, or alternatively causing production of antibodies capable of aberrantly stimulating calcium-sensing receptor (CaSR) of parathyroid gland chief cells [35]. This can result in hypercalcaemia.

The patient had no other history, or features on examination or investigations suggestive of exocrine dysfunction, or systemic manifestations of pSS, which is known to potentially affect almost any organ system and where it derives it's reputation as the Janus-faced disease [25].

Malignancy cannot be ruled out in this case. Lymphoma is common in pSS with a bidirectional association [26]. Prevalence of lymphoma in pSS is reported as 2.6% to 9.8% [27], however the patient's hypercalcemia was longstanding and she had no specific serologic markers, or systemic signs and symptoms suggestive of malignancy, so other possible causes of hypercalcaemia require investigation.

The patient's collapse was considered in the context of possible pSS, however CNS involvement was considered unlikely as the patient's CT brain was unremarkable, she remained conscious throughout admission with resolution of right sided facial numbness and reported no further episodes of collapse, or altered neurological complaints in the two weeks between admission and phone-call follow up. In the absence of pharmacological intervention, CNS involvement of pSS would not spontaneously resolve in such a manner, therefore the authors attributed the patient's presenting compliant of unconscious collapse to IV methamphetamine use and not to the incidental rheumatic pathology discussed here.

Systemic Lupus Erythematosus is a possible differential diagnosis in this case. The patient did present with a collapse that could represent a first seizure. She did not have a history of psychosis, or delirium. The patient did not present with a malar rash. With a normal renal function, absence of antiphospholipid antibodies, Anti smith antibodies, or anti DsDNA antibodies, normal complement levels and absence of leukopenia, thrombocytopenia, or autoimmune haemolysis, absence of oral ulcers, absence of alopecia, this makes the diagnosis less likely. The patient did not meet the 2019 ACR/EULAR Classification Criteria for Systemic Lupus Erythematosus [35] based on the information gathered from tests of this assessment. A score of 10 is required for diagnosis. In addition to the chronicity of the dermatologic lesions, the patient denied any recent infectious symptoms making an acute viral, or bacterial cause of vasculitis unlikely. Chronic causes of infection were considered, the patient tested negative for HCV and HBV.

Although an HIV test was not performed, it was considered less likely as a potential infective agent, however it is important to be aware that HIV is associated with a multitude of rheumatic presentations and that rheumatic/musculoskeletal diseases can be the presenting feature of the illness in up to 30% of cases [28] with an overall prevalence of 45% in HIV-affected individuals [29], therefore it cannot be ruled out entirely.

The patient was not taking any regular, or over the counter medications that could account for the dermatologic lesions in this presentation. The authors reviewed the literature on illicit drug-induced vasculitis. Whilst there is an association with cocaine use when it is contaminated with the anti-worming agent levamisole, a common issue in Australia and other countries [30], this typically is associated with ANCA positive vasculitis although there are case reports of ANCA negative vasculitis as well [31]. The patient's negative ANCA makes this less likely. There is no readily available literature suggesting ice is cut with levamisole in the Australian context. There is a paucity of literature associated with IV ice usage and leukocytoclastic vasculitis with the exception of one report by who mention crystal methamphetamine as a potential theoretical cause of vasculitis. This makes this differential diagnoses less likely than pSS. Cases of pseudo-vasculitis in association with methamphetamine use are reported [32, 33]. Additionally, the patient has been using IV drugs for many years and she reported her rash as being present only in the last 12 months. This would fit more with the onset of pSS in a middle-aged female.

Conditions that were ruled out based on the histological and laboratory tests were RA-associated vasculitis, Hepatitis B and C associated-vasculitis, cutaneous pseudo-vasculitis, IgG4-related disease and amyloidosis. Achieving a formal diagnosis and timely rheumatologic follow up for rheumatic diseases represents a significant challenge in rural Australia where waiting times are long, distances are vast and the majority of rheumatologists are located in metropolitan centres.

Additionally, patients who are intravenous drug users frequently do not prioritise their health and find it logistically challenging to travel to metropolitan centres to seek care.

The authors made the decision to biopsy the lesions, something which is not routinely done in an emergency department setting. However, given the opportunistic benefits for a patient who might be lost to follow up, or who experiences intermittent symptoms that might not be present when the patient presents to their primary care doctor, it was deemed appropriate in this context. Additionally, Australia is currently experiencing a General Practitioner crisis with shortages and long waiting times of several weeks to months and it would not be acceptable to expect a patient to wait so long

in this context.

Emergent and serious rheumatic presentations are frequently encountered in the emergency department where the authors practice, however there are few, or no rheumatology services available for such patients in most rural and remote contexts, meaning the emergency department is often the only place where some patients will present and receive care. This represents a significant challenge for patients and health care professionals operating in these areas.

In this case, the patient was discussed with a rheumatology team at the nearest metropolitan centre, however for many patients travel to metropolitan areas is logistically and financially challenging, resulting in diagnostic delays, or missed diagnosis, reduced access to treatment and poor patient outcomes and is something the authors recognise as an area that requires addressing by the current health model.

Whilst a formal diagnosis is not possible in the absence of a rheumatologic evaluation including objective measures of ocular and oral dryness, based on this discussion the authors are reasonably confident this patient represents a case of pSS with leukocytoclastic vasculitis that was an incidental finding resulting from the patient's presentation to the emergency department.

• pSS can present with a leukocytoclastic vasculitis that might be associated with a peripheral neuropathy
• Certain illicit drugs can produce a vasculitis, or pseudovasculitis
• Patients who present to emergency departments with unusual rashes should be opportunistically biopsied to facilitate timely diagnosis and treatment
• Concurrent vasculitis serology performed in the emergency department at the time of patient presentation is beneficial in assisting with diagnosis
• pSS can result in very high RF titres that should be interpreted in context with other investigations and the clinical presentation to avoid a misdiagnosis of RA
• Hypercalcaemia can occur in pSS
• Nephrolithiasis occurs in 14-32% of patients with pSS
• Further research to establish the relationship between pSS and sarcoidosis is required
• Doctors who work in emergency departments could benefit from education to raise clinical awareness of pSS and the relationship between nephrolithiasis, vasculitis and pSS

Table 3. Key Learning Points

4. Conclusion:

Although the patient's vasculitis serology was incomplete there is enough clinical, serological and histological evidence to suggest the most likely diagnosis of leukocytoclastic vasculitis in the context of pSS. The histological and immunofluorescent findings, the positive ANA of 1:2650 with presence of anti SSA antibodies, the very high RF, hypercalcaemia with history of nephrolithiasis and hypergammaglobulinemia and the patient's history and reported symptoms all support a diagnosis of pSS.

Differential diagnosis including illicit-drug related cutaneous vasculitis were considered, but are less likely for the reasons discussed.

This case highlights the importance of opportunistic biopsy in the context of rural medicine, especially in patients with demographics that do not engage well with follow up.

There are very limited resources in rural contexts for rheumatology diagnosis and management and the emergency department can play an important role for improved recognition, referral and positive outcome of such patients.

Conflict of Interests:

The authors have no conflict of interests to declare. No funding was received for the authoring, or publication of this paper.

Patient Consent:

The authors obtained patient consent for use of photographs and information and approval from the hospital CEO for the authoring and publication of this paper

Contributors:

The primary author contributed to the conception and design of the work, drafted the manuscript and conducted the literature review. The secondary author revised the paper for important intellectual content and critical evaluation. Both authors give final approval of the version to be published and agreed to be accountable for all aspects of the work.

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