 DOI: https://doi.org/10.4038/jccp.v56i2.8112

From joint pain to granuloma – An interactive diagnostic journey

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Journal of the Ceylon College of Physicians, 2025, **56**, 138-143

Introduction

Clinical Challenge is a new feature of the journal aimed at supporting everyday clinical practice through real patient stories. Each case is presented with a step-by-step guide with reasoning behind investigations and management decisions, with a focus on rational and cost-effective care in resource-limited healthcare settings.

In this issue, we share the story of Mrs. K, a 60-year-old retired teacher who presented with progressively painful swelling of both legs. Initially managed as cellulitis, her lack of response to antibiotics and the subsequent development of tender erythematous nodules created a diagnostic dilemma. This case highlights the value of careful clinical assessment, reflection, and rational use of available investigations in routine clinical practice.

Case presentation: The initial encounter

Mrs K, a 60-year-old retired teacher, was admitted to our medical ward with painful swelling of her legs. Over the last month, she had developed progressive bilateral lower limb swelling that extended from her feet to her knees. This was accompanied by erythema and severe aching pain, which significantly impaired her mobility. She had initially been treated at a local hospital for presumed bilateral cellulitis with a 10-day course of flucloxacillin, but her symptoms not only persisted but worsened. Multiple tender, erythematous nodules appeared on both legs without ulceration, causing her considerable distress.

The swelling and nodules were accompanied by systemic symptoms, including fatigue, loss of appetite, and polyarthralgia, mainly affecting her knees and ankles. Notably, there were no fever, weight loss, cough, respiratory symptoms, or gastrointestinal upset. There was no history of recent travel, exposure to tuberculosis, or significant past medical illnesses.

On physical examination, the patient appeared comfortable with normal vital signs. Her lower limbs showed bilateral pitting ankle oedema with tender, erythematous nodules (Figure 1) over the anterior shins without necrosis or ulceration. The cardiovascular, respiratory, and abdominal examinations were entirely unremarkable.

Clinical pause: Your initial assessment

Before reading further, take a moment to consider what you would do in this situation. What is your working diagnosis for the skin lesions? What are your top three differential diagnoses for the overall presentation? Given this is a resource-limited setting, what would your first investigation be?

Diagnostic reasoning: The clinical debate

The attending team immediately recognised the classic appearance of erythema nodosum, which led to an important clinical discussion that would shape our entire approach. While erythema nodosum can often be dismissed as a mere dermatological condition, it should prompt an investigation for systemic diseases, particularly when accompanied by constitutional symptoms, as in this patient.[1,2]

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Received 10 September 2025, accepted 20 October 2025.

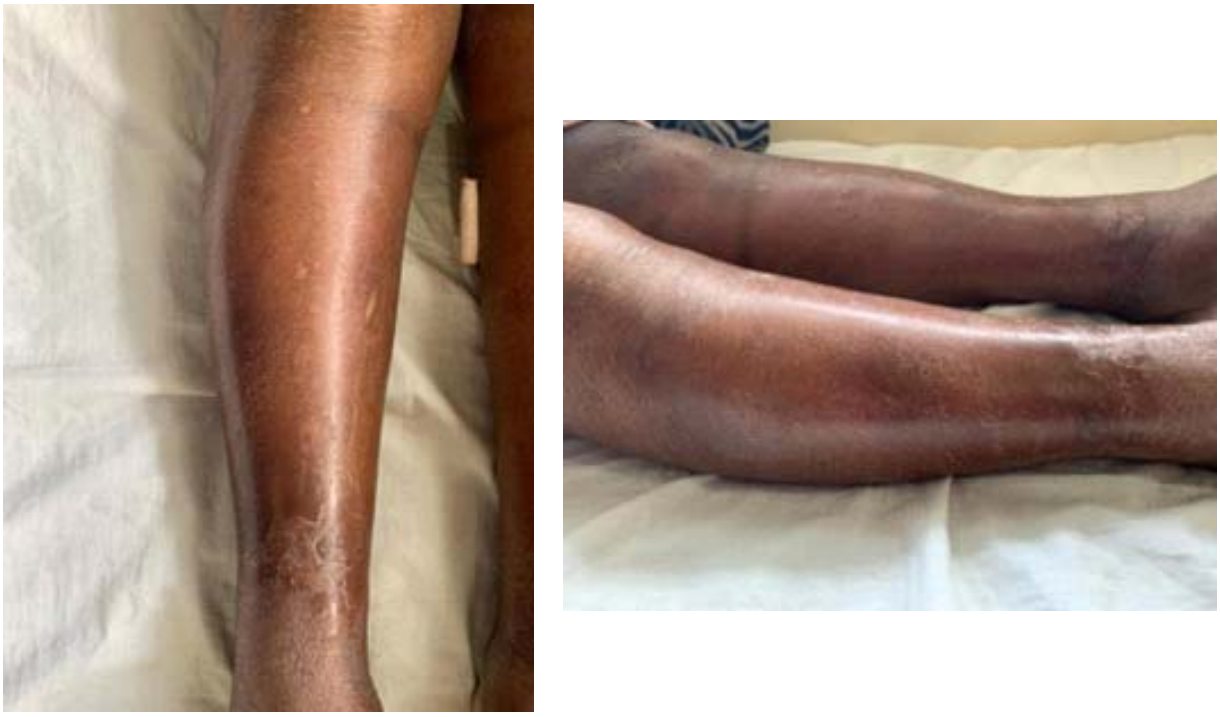

Figure 1. Erythematous nodules on the shins.

Our differential diagnosis was organised into three broad categories, each requiring different investigative approaches. Infectious causes were particularly significant given the high prevalence of certain communicable diseases in Sri Lanka. Tuberculosis has an incidence of 62 per 100,000 population in our setting, making it a constant consideration[3]. We also needed to consider streptococcal infections, atypical infections such as *Mycoplasma pneumoniae,* and fungal infections.

Autoimmune diseases formed our second major category. Sarcoidosis is increasingly recognised in South Asian populations and was a potential diagnosis.[4] We also considered inflammatory bowel disease and systemic vasculitis as possible underlying causes.

The third category, malignancy, was perhaps our most significant concern given Mrs K's age and constitutional symptoms. Both lymphoproliferative disorders and solid organ malignancies needed to be excluded urgently.

Investigation strategy: Resource-conscious approach

We began with first-line investigations that would provide the most information at the lowest cost. The laboratory results showed a markedly elevated ESR of 110 mm in the first hour, confirming significant systemic inflammation. The complete blood count, renal function, and liver function tests were all normal, which was reassuring but did not significantly narrow our differential diagnosis.

At this point, with classical erythematous nodules on both shins, the team faced a practical question: should a skin biopsy be performed? A biopsy can confirm the diagnosis of erythema nodosum histologically and help exclude mimics, such as nodular vasculitis, panniculitis, or cutaneous lymphoma. In some cases, it can also provide histological clues to systemic diseases such as sarcoidosis or tuberculosis. Arguments against performing a biopsy included the typical clinical appearance of erythema nodosum, the inability of a biopsy to identify the underlying cause definitively, and the fact that, in a resource-limited setting, avoiding unnecessary procedures saves time and cost.

We attempted a skin biopsy, but it did not include adequate subcutaneous tissue, rendering the result non-diagnostic. A skin biopsy is advised when the diagnosis of erythema nodosum is uncertain; however, in this case, the lesions were strongly suggestive clinically, so histological confirmation was not deemed necessary. As the biopsy would not provide an aetiological diagnosis, repeating the procedure would

only delay further evaluation. Given the classic clinical features and the urgent need to exclude malignancy in this age group, we decided to prioritise identifying the underlying aetiology rather than confirming what was already strongly suspected clinically.

The next crucial decision was selecting our imaging strategy, considering costs, availability, and diagnostic effectiveness. The chest X-ray is inexpensive, readily available, has a high diagnostic yield for tuberculosis and sarcoidosis, and could be performed on the same day. Similarly, abdominal ultrasound is readily accessible, has a moderate diagnostic yield, and can be completed the same day. In contrast, a CT scan of the chest and a CT scan of the abdomen, though offering a very high diagnostic accuracy, is considerably more expensive, less readily available, and would require 2-3 days to complete. Given Sri Lanka's tuberculosis burden and the classical association between erythema nodosum and thoracic disease, chest radiography represented the most rational first step. The chest X-ray revealed subtle but significant right hilar lymphadenopathy (Figure 2) without consolidation or pneumonia. This single finding completely changed our approach to managing the patient.

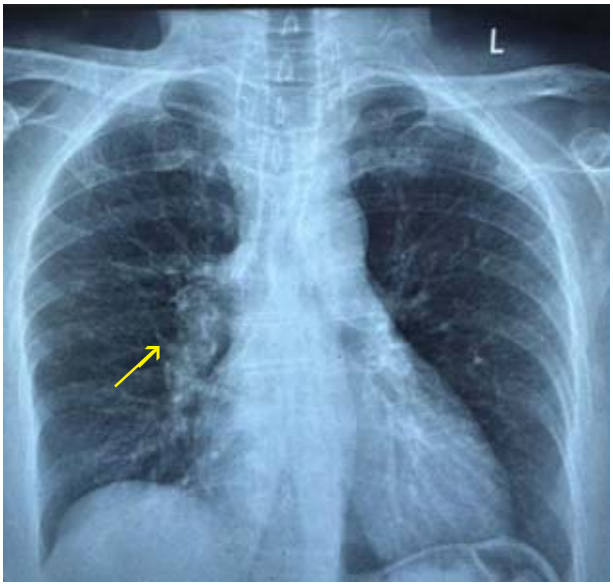

Figure 2. Chest radiograph showing mild right hilar lymphadenopathy.

The combination of hilar lymphadenopathy with erythema nodosum led to a more focused differential diagnosis. Sarcoidosis, especially presenting as Löfgren's syndrome, became highly probable.[2] Tuberculosis remained important given its endemic setting. Lymphoma was still a notable concern considering her age group. Fungal infections appeared less likely given her limited geographic exposure, as did other systemic diseases.

An ultrasound of the abdomen performed at this stage was normal, showing no intra-abdominal lymphadenopathy and no hepatosplenomegaly.

Systematic exclusion process

We proceeded systematically to exclude infectious causes. HIV serology, VDRL, and blood cultures were all negative. We obtained three serial sputum samples for acid-fast bacilli, all of which were negative. The Mantoux test was also negative. Anti-streptolysin O titres were normal, ruling out a recent streptococcal infection. For autoimmune screening, both rheumatoid factor and antinuclear antibodies returned negative.

Despite this comprehensive infectious disease workup, we recognised that we could not definitively rule out tuberculosis. In the Sri Lankan setting, negative sputum AFB does not exclude pulmonary tuberculosis, particularly when there is mediastinal involvement.[5] To further investigate the possibility of sarcoidosis, serum calcium levels were assessed, and they were repeatedly normal. Angiotensin-converting enzyme (ACE) testing was not performed due to financial constraints, as the test remains prohibitively expensive in resource-limited settings.

Advanced imaging: Defining the pattern

With our clinical suspicion focused on sarcoidosis versus lymphoma, we proceeded to a high-resolution CT scan of the chest. This revealed bilateral mediastinal lymphadenopathy without pulmonary parenchymal involvement (Figure 3), a pattern that is highly suggestive of early-stage sarcoidosis.[6]

To assess for systemic involvement, we performed contrast-enhanced CT of the chest, abdomen, and pelvis. This revealed multiple para-aortic and mediastinal nodal enlargements with hepatic infiltration, confirming that this was indeed a systemic process rather than isolated thoracic disease (Figure 4).

At this point, we faced another critical decision regarding tissue diagnosis. With imaging suggesting either sarcoidosis or lymphoma, definitive histological confirmation became essential. We considered several options: bronchoscopy with biopsy would be less invasive, while CT-guided biopsy would be moderately invasive. Video-assisted thoracoscopic surgery (VATS) would be the most invasive option but would provide the highest diagnostic yield.

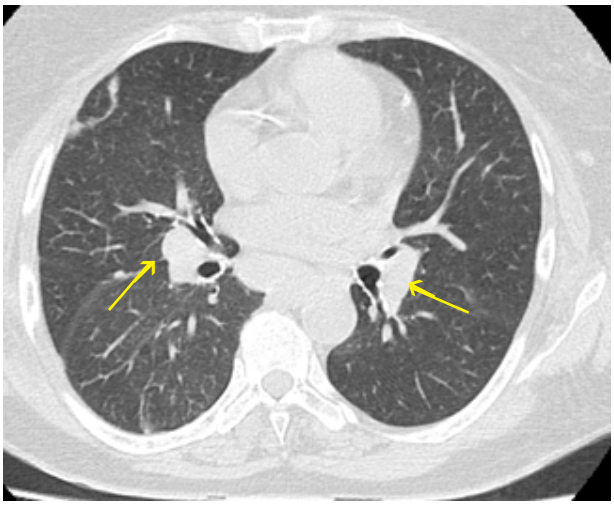

Figure 3. HRCT of the chest showing bilateral mediastinal lymphadenopathy.

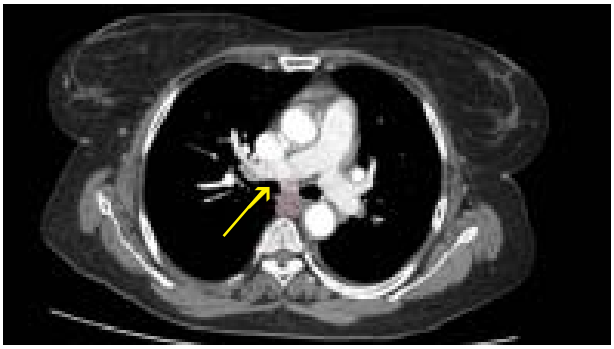

Figure 4. CECT of chest and abdomen showing multiple para-aortic and mediastinal nodal enlargements.

The diagnostic resolution

Mediastinal lymph node biopsy obtained through VATS revealed the pathognomonic features we had been seeking. Histopathological examination revealed a non-caseating granuloma composed of aggregated epithelioid histiocytes and multinucleated giant cells with a scant lymphocytic cuff (Figure 5A and 5B). Notably, there was no caseation or necrosis, which effectively excluded tuberculosis, and no malignant cells were visible.

Final diagnosis: Sarcoidosis with Löfgren's Syndrome

With the histopathological confirmation, we were able to make the definitive diagnosis of sarcoidosis presenting as Löfgren's syndrome. Mrs K had the classic tetrad: bilateral hilar lymphadenopathy, erythema nodosum, polyarthralgia, and constitutional symptoms.

Treatment and outcomes

The diagnosis of Löfgren's syndrome had important therapeutic implications. While many cases of Löfgren's syndrome resolve spontaneously, Mrs K's disabling arthritis was significantly impacting her quality of life. After consultation with rheumatology colleagues, we initiated systemic corticosteroids with prednisolone 30mg daily, planning a gradual taper over 6-12 months.[6]

The response to treatment followed a predictable timeline. By the first week, there was a modest improvement in her joint pain. By the third week, a significant improvement was observed in both her arthralgia and mobility. At six weeks, there was near-complete resolution of the erythema nodosum lesions. A follow-up CT scan at three months showed stable mediastinal lymphadenopathy, as expected and reassuring.

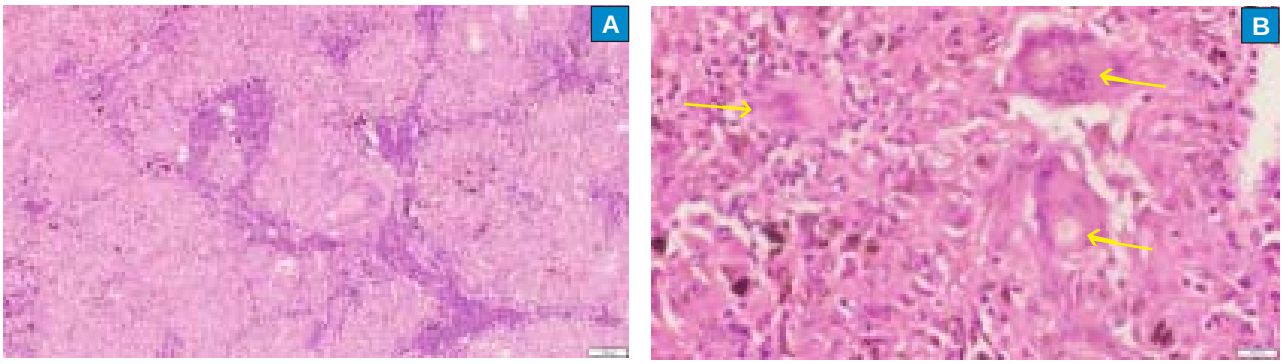

Figure 5A and 5B. Histopathology of lymph node showing non-caseating granuloma composed of aggregated epithelioid histiocytes and multinucleated giant cells.

We established a comprehensive monitoring protocol given the systemic nature of sarcoidosis. This included clinical assessment every 3 months initially, chest imaging every 6 months for the first year, ophthalmological screening every 6 months to monitor for uveitis, pulmonary function tests if respiratory symptoms developed, and cardiac evaluation if indicated.[6]

Key learning points

This case reinforced several important clinical principles, particularly relevant to practice in resource-limited settings. The combination of erythema nodosum with hilar lymphadenopathy should immediately suggest sarcoidosis in the appropriate clinical context.[2] Simple, cost-effective investigations like chest X-ray can offer significant diagnostic value when used in the appropriate clinical context.

The importance of considering local epidemiology became evident throughout our approach. In Sri Lanka, tuberculosis must always be considered when evaluating granulomatous diseases.[7] However, sarcoidosis is increasingly recognised in South Asian populations,[4] and cost considerations greatly influence diagnostic pathways that may be less relevant in resource-rich settings.

The prognostic implications of specifically diagnosing Löfgren's syndrome were crucial for Mrs K and her family. This variant of sarcoidosis carries an excellent prognosis, with 80-90% of patients achieving spontaneous remission within two years, a recurrence rate of less than 5%, and a low risk of chronic organ damage.[2,8]

System-level insights

This case required multidisciplinary collaboration involving expertise from internal medicine for clinical assessment, radiology for imaging interpretation, thoracic surgery for the VATS procedure, pathology for histological diagnosis, and rheumatology for treatment optimisation. This collaborative approach is essential for complex cases but requires coordination that can be challenging in resource-limited settings.

We learned important lessons about resource optimisation strategies. Starting with high-yield, low-cost investigations makes both clinical and economic sense. Considering local disease prevalence in differential diagnosis helps to focus investigations appropriately. Using clinical pattern recognition to guide the investigation sequence prevents unnecessary testing.

Alternative scenarios: "What if" analysis

We reflected on how this case might have proceeded under different circumstances. If CT had not been available, we would have proceeded to bronchoscopy based on the chest X-ray findings. If VATS capability had not been available, we could have considered transbronchial biopsy. We might even have considered an empirical anti-tuberculosis treatment trial before invasive procedures, if the necessary resources had not been available.

If the clinical presentation and/or initial investigation results had been different, our approach would have changed accordingly. A normal chest X-ray would have led us to focus on abdominal imaging and inflammatory markers. The presence of fever would have led us to prioritise infectious disease workup more aggressively. In a younger patient, we would have given greater consideration to inflammatory bowel disease, even in the absence of gastrointestinal symptoms.

Conclusion: Lessons for clinical practice

This case exemplifies several crucial principles for practising medicine in resource-limited settings. From a clinical excellence perspective, it demonstrates the value of a systematic approach moving from simple to complex investigations, the importance of pattern recognition and syndrome identification, and the need to integrate local epidemiological factors into clinical decision-making. From a resource stewardship standpoint, it shows how cost-effective investigation sequencing can be both economically and clinically sound. It illustrates the appropriate use of advanced imaging and procedures, highlighting the importance of patient-centred economic decision-making in healthcare delivery.

The holistic care aspects included understanding patient and family perspectives throughout the process, maintaining clear communication about diagnosis and prognosis, and establishing appropriate long-term monitoring and support systems. The identification of Löfgren's syndrome provided not just diagnostic clarity but also crucial prognostic reassurance for Mrs K and her family. This case demonstrates that excellent clinical care can be delivered in resource-constrained settings through thoughtful clinical reasoning, appropriate investigation sequencing, and effective multidisciplinary collaboration.[2,8]

For practitioners in Sri Lanka and similar settings, this case underscores the importance of maintaining a broad differential diagnosis while being mindful of local disease patterns and economic realities. The

systematic approach we employed and the favourable outcome we achieved underscore the importance of clinical pattern recognition and evidence-based practice in improving patient care, regardless of resource limitations.

Author declaration

Conflict of interests

The authors declare no conflict of interests.

Patient consent

Written informed consent was obtained from the patient for publication of this clinical practice and accompanying images.

Data availability

Data supporting this clinical practice are available from the corresponding author upon reasonable request.

Acknowledgements

We would like to thank the patient for allowing us to share this story with our colleagues.

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