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CASE REPORT

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Idiopathic recurrent serositis—Off the beaten track

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Abstract

A 63-year-old female presented with chest pain and fever, and was found to have recurrent pleuropericardial effusions. Extensive investigations including infection screen and serologies, autoimmune screen and pleural and pericardial biopsy revealed no secondary aetiologies. She was diagnosed with idiopathic recurrent serositis (IRS). Our patient developed rash to naproxen, so she was started on colchicine monotherapy and responded well clinically. A review of the literature demonstrated that pleuropericardial effusions are rare occurrences, with patients occasionally being perceived as a medical enigma. This case study recommends an approach to guide physicians in their diagnosis and management of patients with pleuropericardial syndrome. Our case had an inflammatory phenotype, either autoimmune or seronegative serositis of unclear aetiology, which was recurrent and required pharmacological treatment. While the treatment for IRS lies in combined therapy with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and colchicine, monotherapy with colchicine was effective in the treatment and preventing recurrence in our unique case.

KEYWORDS
effusion, pleuropericardial, recurrent, serositis

INTRODUCTION

Serositis, which is the inflammation of serous tissues often presenting as effusions, is often linked to infectious, neoplastic and rheumatological causes.[1] In rare cases, no aetiology is ever identified, leading to the diagnosis of idiopathic serositis. An extensive search of the literature revealed limited information surrounding idiopathic recurrent serositis (IRS), suggesting the rarity of this condition. Considering the lack of scholarship surrounding this diagnosis, there is a paucity of resources to guide physicians in their management plan. Through our case study, we summarize our approach in the diagnostic and management process of our patient.

CASE REPORT

A 63-year-old Chinese female, with a past medical history only significant for melasma, presented to the emergency department with a 3-day history of worsening left-sided, non-radiating chest pain, associated with shortness of breath and nausea. On examination, there were normal heart sounds and lungs clear with equal breath sounds bilaterally. Electrocardiogram showed no ischaemic changes. Vitals were normal. On imaging, chest x-ray (CXR) showed mild blunting of bilateral costophrenic angles (Figure 1). Computed tomography (CT) of the thorax revealed small left pleural effusion and mild focal consolidation of the left lower lobe (Figure 2).

Initial white blood cell (WBC) level was elevated at $14.5 \times 10^3/\mu l$ while the peripheral eosinophil count was zero. C-reactive protein (CRP) was elevated at 165 mg/L, procalcitonin was 0.06 mcg/L and pro-Brain Natriuretic protein was 309 pg/ml. She was treated with intravenous Amoxicillin/Clavulanic acid, based on the preliminary diagnosis of pneumonia with left parapneumonic effusion. However, she had persistent temperature spikes and repeat CXR on day 6 of admission showed moderate left pleural effusion. She underwent left chest drain insertion. Laboratory analysis of the fluid

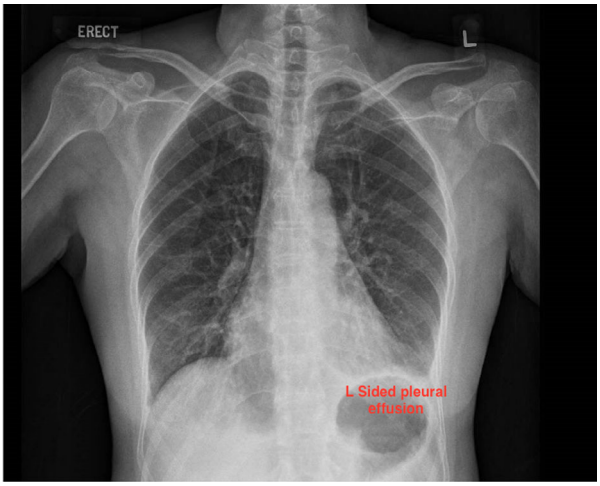

FIGURE 1 Chest x-ray on admission

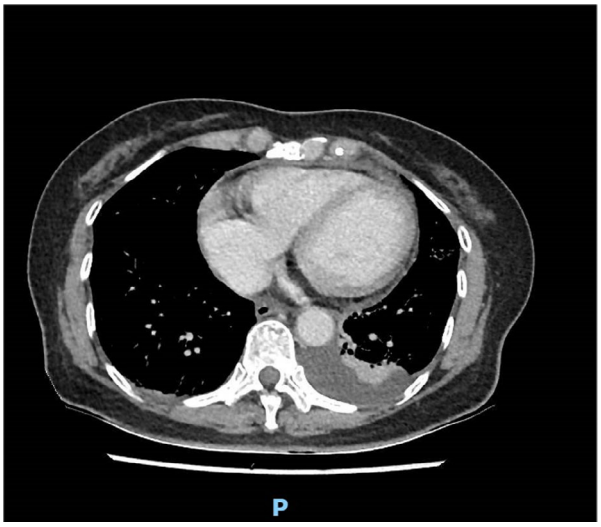

FIGURE 2 Computed tomography of the chest on admission

drained revealed an exudative picture with lymphocytic predominance (90%) and the pleural/serum protein ratio was 0.53 (pleural fluid protein 40.6 g/L, serum protein level 76 g/L, pleural pH 7.65, glucose 7.8 mmol/L, Adenosine Deaminase (ADA) 4.0 U/L). Pleural fluid culture was negative. She felt symptomatically better and was discharged home.

The patient was readmitted 4 days later with a 2-day history of recurrent left-sided chest pain. WBC level was elevated at 20.4 $\times 10^3$/μl. Repeat CXR showed moderate left and small right pleural effusion (Figure 3). CRP increased to 266 mg/L, while erythrocyte sedimentation rate was 112 mm/h. Echocardiography revealed a new moderate pericardial effusion, with no features suggestive of constrictive pericarditis or tamponade. CT of the thorax, abdomen and pelvis showed bilateral moderate pleural effusions, interval pericardial effusion with pericardial thickening and enhancement suggestive of pericarditis (Figure 4).

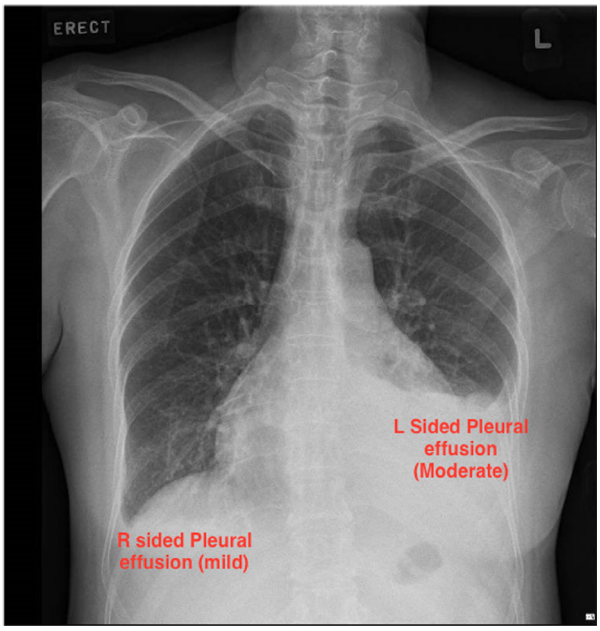

FIGURE 3 Recurrent pleural effusion

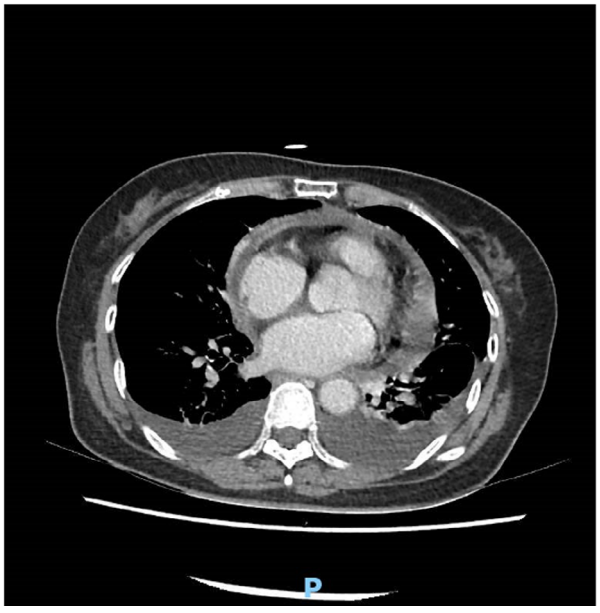

FIGURE 4 Recurrent pleural effusion on computed tomography of the chest

Autoimmune screen (rheumatoid factor, anti-cyclic citrullinated peptides, Anti-nuclear antigens, Extractable nuclear antigen, Antineutrophil cytoplastic antibodies) was negative. Anti-double stranded DNA was also negative at 3.77 IU. Lupus anticoagulant had a borderline result. IgG subclasses were normal. Microbiology (Coxiella/Rickettsia/dengue/HIV) was negative. Positron emission tomography-CT did not show any concerning hypermetabolic areas.

She subsequently had a right video-assisted thoracoscopic surgery pleural and pericardial biopsy. Intraoperatively, the

TABLE 1 Summary of investigations

Investigation		Result
Full blood count		WCC elevated at 20.4 × 10^3/μl
Serum LDH		209 U/L
Serum protein		76 g/L
Autoimmune	Anti-double-stranded (DNA) antibody	3.77 (Negative)
	Anti-smooth muscle	Negative
	M2	2.0 (Negative)
	LKM-1	1.0 (Negative)
	LC-1	2.0 (Negative)
	Anti-soluble liver antigen/Liver -Pancrease (SLA/LP)	3.0 (Negative)
	Anti nuclear antigen	Negative
	Antineutrophil cytoplasmic antigen	Negative
	Smith antibody	<1.0
	Ribonucleoprotein antibody	<1.0
	Ro (SSA) antibody	<1.0
	La (SSB) antibody	<1.0
	Sd 70 antibody	<1.0
	Jo-1 antibody	<1.0
	Anti-cardiolipin IgG antibody	1.6 GPL U/ml (Negative)
	Anti-cardiolipin IgM antibody	0.3 GPL U/ml (Negative)
	Lupus anticoagulant	Borderline result
IgG subclasses		Normal
Infectious disease screen		
Pneumococcus antigen test		All negative
Urine Legionella antigen test		
T-SPOT TB		
Coxiella burnetii total antibody		
Lower respiratory culture		
Rickettsia serology panel		
Hepatitis C antibody screen (Enzyme immunoassay)		
Hepatitis B surface antigen (qualitative)		
Hepatitis B Surface antibody (anti-HBs)		
SARS-CoV-2 PCR		
Respiratory virus multiplex		
Hepatitis E IgM Antibody		
Hepatitis A IgM Antibody		
HIV screen		
Cytomegalovirus PCR		
Dengue IgM		
Dengue IgG		
Herpes simplex virus IgM antibody		
Epstein–Barr virus capsid Ag IgM Ab		
CMQ quantitative PCR		
Dengue virus NS1 antigen		
Mesothelial cell analysis		Strongly diffusely positive for calretinin and D2-40
		Nuclear positivity to WT-1
		BerEp4 negative

(Continues)

TABLE 1 (Continued)

Investigation	Result
Pleural fluid analysis	Appearance: yellow and slightly turbid
	90% Lymphocytes
	Fluid LDH 102 U/L
	Fluid glucose 7.8 mmol/L
	Fluid protein 40.6 g/L
	ADA 4.0 U/L pH 7.65
Pleural and pericardial microbiology	All negative
Pleural biopsy	Reactive mesothelial proliferation
	No granulomatous inflammation
	No evidence of lymphoplasmacytic pleuritis
Pericardial biopsy	Fibrinous exudates
Imaging	CXR: Mild blunting of bilateral costophrenic angles
	Chest CT: Left pleural effusion Mild focal consolidation in the left lower lobe
	Echocardiogram: Pericardial effusion (Moderate)

Abbreviations: ADA, adenosine deaminase; ANA, anti-nuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; CT, computed tomography; CXR, chest x-ray; EIA, enzyme immunoassay; LDH, lactate dehydrogenase; MRSA, methylcillin-resistant *Staphylococcus Aureus*; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SLA/LP, soluble liver antigen/liver-pancreas; WCC, white cell count.

left chest tube inserted drained serous fluid. Right pleura had no obvious lesion and serous fluid was drained. Pericardium was thickened with moderate fibrinous tissue beneath and very minimal pericardial effusion. Rest of the lung, pleura and diaphragm were normal. Pericardial window was created, and fibrinous tissue was removed as much as possible.

Cytology of pleural fluid, which appeared grossly as slightly turbid yellowish fluid, showed a mixed yield of reactive mesothelial cells, scattered lymphocytes and neutrophils. Malignant cells were negative. Pleural and pericardium bacterial, acid-fast bacilli and fungal cultures were also negative Pleural biopsy revealed reactive mesothelial proliferation with no granulomatous inflammation or evidence of lymphoplasmacytic pleuritis, while pericardial biopsy showed fibrinous exudates. Microscopic analysis revealed focal mesothelial proliferation consisting of cuboidal cells with mildly enlarged nuclei and prominent nucleoli in a single row and slightly nested focally but without evidence of invasion into deep stroma. These cells were strongly and diffusely positive for calretinin and D2-40 and showed nuclear positivity to WT-1. BerEp4 was negative. There was no loss of BAP1 nuclear staining, no positivity for EMA and desmin demonstrated positive staining within the mesothelial cells. Fluorescence in situ hybridization (FISH) studies demonstrated no homozygous deletion of CDKN2A (Table 1).

Twelve days after the biopsy, the patient had recurrence of fever with elevated WBC/neutrophils/CRP and associated mild transaminitis. Her CXR showed recurrence of left-sided pleural effusion. She was started on naproxen but developed rash, so was switched to monotherapy of colchicine 500 mcg twice daily. There was improvement in her symptoms and her laboratory results improved. This was confirmed with a CXR that showed resolution of the pleural effusions (Figure 5). She was on colchicine for about 16 weeks. At 1-year follow-up, she was asymptomatic and CXR showed no recurrence (Table 2).

DISCUSSION

IRS is described to be inflammation of serous membranes in the absence of any apparent triggering disease. It has been proposed to be of an autoinflammatory origin, resulting from a dysregulated immune response; however, its exact pathogenesis remains unclear.[2] Despite limited research on IRS, its presentation remains a common occurrence in medicine.

Non-specific pleuritis (NSP) is defined as fibrinous or inflammatory pleuritis which cannot be attributed to a specific benign or malignant aetiology.[3] A comparative study amongst patients previously diagnosed with NSP concluded that the majority of patients had a probable cause of pleuritis identified; thus, true NSP occurs in only a minority (25%) of patients.[4]

Our patient had undergone an extensive work-up that ruled out secondary aetiologies and probable causes for the pleuritis. The patient's presentation of pyrexia and laboratory results of a raised CRP merely confirmed the inflammatory phenotype of the exudate, either autoimmune or seronegative inflammatory serositis of unclear aetiology.

TABLE 2 Light's criteria

	Transudate	Exudate
Pleural fluid protein/ serum protein	≤0.5	>0.5
Pleural fluid LDH/ serum LDH	≤0.6	>0.6
Pleural LDH	≤2/3 of the upper limit of normal	>2/3 of the upper limit of normal

Abbreviation: LDH, lactate dehydrogenase.

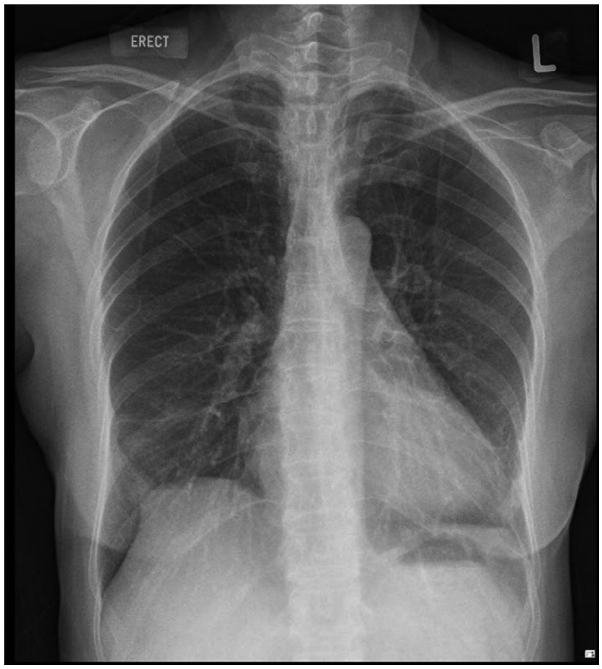

FIGURE 5 Resolution of pleural effusion following colchicine therapy

Additionally, the persistence despite using antibiotics further suggests a non-infective cause. Rather than a truly idiopathic pleuritis or clinical NSP, she had an underlying inflammatory phenotype.

Primary therapy with glucocorticoids for acute and recurrent idiopathic pericarditis was associated with a high rate of relapse when the steroid was stopped or tapered and appears to blunt the efficacy of colchicine in preventing recurrences.[5] A case report by Lilly for recurrent pericarditis included treatment with NSAIDs and colchicine for 3 weeks, followed by colchicine monotherapy for 6 months.[6]

Massaro et al. studied the therapeutic management of IRS (involving inflammatory/autoimmune serositis) and found that a reduced duration of therapy with steroids and a longer duration of NSAIDs therapy have longer disease-free survival. An earlier combination therapy of colchicine with NSAIDs or steroids was associated with a decrease in recurrence rates.[2] Although the role of glucocorticoids in the suppression of inflammation is well recognized and has been shown to be effective in prompt resolution of serositis,[6] its use was not employed in the management of our patient amidst concern during the work-up that steroids may mask the potential diagnoses such as lymphoma. In view of NSAID allergy, colchicine monotherapy showed effectiveness in the management of our patient.

Connective tissue diseases such as rheumatoid arthritis and systemic lupus erythematosus can present with pleural pathology in approximately 5%–20% and 17%–60% of cases, respectively,[7] and most effusions resolve spontaneously. Corticosteroids may be administered in cases of persistent effusion to aid resolution. This case of IRS however represents an inflammatory phenotype where spontaneous resolution did not occur, requiring pharmacological treatment.

Clinicians are reminded to consider a diversity of differentials, refined by a focused history and examination, and finally to interpret all findings in each unique clinical context. It is important to rule out secondary aetiologies prior to a diagnosis of IRS. Our case had an inflammatory phenotype, either autoimmune or seronegative serositis of unclear aetiology. Although combined therapy with colchicine and NSAIDs is the first-line treatment for IRS, our unique case study using colchicine monotherapy shows that this can be considered to lower the risk of recurrence.

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CONFLICT OF INTEREST

None declared.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this case report and accompanying images.

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