

Polyserositis secondary to COVID-19: the diagnostic dilemma

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SUMMARY

COVID-19 is a novel disease often presenting with a cough, fever or a change in smell or taste. Recently, it has been recognised that COVID-19 may result in multisystemic issues and thus cause atypical symptoms, which can cause diagnostic delay, uncertainty and inaccuracy. A 60-year-old woman presented to the hospital with a 2-day history of mid-thoracic discomfort, intermittent rigours, fevers and general malaise, a few weeks after likely COVID-19 infection. She was admitted and treated for community-acquired pneumonia. However, her symptoms recurred despite multiple courses of antibiotics, which prompted further workup. A combination of a pleural and pericardial effusion was identified, leading to a diagnosis of polyserositis, and a COVID-19 antibody test came back positive. Colchicine was effective at resolving her symptoms, leading to further conviction of a probable postviral polyserositis.

BACKGROUND

COVID-19, caused by the novel coronavirus SARS-CoV-2, classically presents with a dry cough, sore throat or shortness of breath. Constitutional symptoms such as headache, fever and myalgia also predominate. However, it is not just a disease confined to the respiratory system; other complications include thrombosis, a change in smell or taste, and even chilblain-like features of the toes. We report on the diagnostic and therapeutic challenges of an unusual case of polyserositis deemed to be secondary to COVID-19 and its implications for other patients who may present with similar symptoms. It took many admissions and consultations to get the final diagnosis—with greater awareness of the range of issues COVID-19 can cause, we hope this delay will be mitigated in the future.

CASE PRESENTATION

A 60-year-old Caucasian woman presented to A&E in April 2020 with a 2-day history of left-sided pleuritic discomfort, intermittent rigours, fevers and general malaise, with an ongoing dry cough. She had no shortness of breath, no palpitations, no peripheral oedema, no rash and no urinary symptoms. She had previously had a dry cough with febrile episodes and loss of taste 3 weeks prior to this presentation. She had a medical history of essential hypertension, previous ablation for supraventricular tachycardia, a tissue aortic valve replacement and paroxysmal atrial fibrillation. She was fully independent in her activities of daily living and lived with her husband. She was an ex-smoker with occasional alcohol intake.

On examination, she had a temperature of 38.5°C, but other observations were within normal parameters. A cardiovascular exam revealed a quiet non-radiating ejection systolic murmur at the left sternal edge; her respiratory exam was normal; and her abdomen was soft and non-tender.

INVESTIGATIONS

Her admission blood tests showed a borderline raised white blood cell count of $10.5 \times 10^9/L$ with neutrophilia of $8.0 \times 10^9/L$. She had a raised C reactive protein (CRP) of 136 mg/L and deranged liver function tests (LFTs), alkaline phosphatase (ALP) of 142 IU/L, bilirubin of $21 \mu\text{mol/L}$ and alanine aminotransferase (ALT) of 28 IU/L, but other biochemical markers including renal function, electrolytes and troponin were within normal limits. An ECG was performed, which showed sinus rhythm with no acute or dynamic changes. The only abnormality on chest X-ray was a small left-sided pleural effusion. She had an echocardiogram which showed pericardial fluid, and therefore a chest CT was requested to further clarify this. The CT reported a 9 mm deep pericardial effusion and a trivial left pleural effusion with a thin rim of fluid around the ascending aorta and borderline mediastinal lymph nodes, likely to be reactive. During this same admission, a transoesophageal echocardiogram was performed, which showed no evidence of endocarditis.

Over the course of her admission, repeat blood tests showed a further increase in CRP to 253 mg/L, and a subsequent chest X-ray was performed and showed new shadowing in the left base and an increase in left pleural fluid. Further testing for an infectious aetiology yielded negative results. This included two sets of blood cultures including those for *Mycobacterium tuberculosis*; viral throat swab for common respiratory pathogens including *Mycoplasma*, influenza viruses A and B, and human metapneumovirus; and serology including enterovirus, parvovirus and influenza. An autoantibody screen for antinuclear antibodies (ANA) and Anti-neutrophil cytoplasmic antibody (ANCA) was also negative.

She was initially treated with vancomycin, gentamicin and rifampicin for possible endocarditis. This was subsequently discontinued after 2 days given the absence of valvular vegetations on transthoracic and transoesophageal echocardiography. A working diagnosis of community-acquired pneumonia was made, and she received a 5-day course of amoxicillin and doxycycline, which resulted in clinical improvement and biochemical resolution of the



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Case report

deranged CRP and LFTs. Her SARS-CoV-2 PCR was negative on multiple occasions during her admission.

The patient was reviewed in the ambulatory medical unit 3 weeks after discharge. On cessation of her initial course of antibiotics, she had started to feel unwell again and was therefore given another course of antibiotics from her general practitioner. This again led to clinical improvement. She relapsed for the second time on cessation of the antibiotics with drenching night sweats and a high fever. On examination, left-sided basal crackles were heard, with a respiration rate of 20 breaths/min and oxygen saturations of 94% on air. Her abdomen was soft and non-tender with no peripheral oedema. Her blood test results showed a white blood cell count of $5.4 \times 10^9/L$, a CRP of 136 and deranged LFTs (ALP 277 IU/L, bilirubin $10 \mu\text{mol/L}$ and ALT 136 IU/L). Blood cultures were repeated, again yielding no bacterial growth. A further chest X-ray showed unchanged left basal consolidation and effusion. She was therefore started on oral co-amoxiclav and clarithromycin for an atypical pneumonia and was discharged with outpatient follow-up planned.

At her follow-up review, her CRP had improved (163 mg/L to 24 mg/L) and LFTs also showed an improvement. She was advised to complete an extended 10-day course of antibiotics.

Four days after finishing the 10-day course of antibiotics, she was reviewed again on the ambulatory unit with persistent episodes of fever associated with rigours, tachycardia, lethargy, fatigue, discomfort under her left breast and an intermittent dry cough. On examination, her chest was clear and her abdomen was soft and non-tender. Her inflammatory markers had again increased, with a CRP of 363 mg/L. Repeat blood cultures and a urine serology, including *Pneumococcus* and *Legionella* antigen testing, were negative. Toxoplasmosis and Q fever serology was also investigated with negative results. She underwent CTs of the chest, abdomen and pelvis, which demonstrated a persistent small pericardial effusion of 9 mm, but otherwise, the upper airway, lungs and pleural spaces were clear. A full body positron emission tomography-CT (PET-CT) showed low-grade uptake within small left pleural and pericardial effusions.

Reassured by the PET-CT, malignancy was considered unlikely, and the biochemical picture also made connective tissue disease unlikely. Given the symptoms 3 weeks prior to her initial presentation, her COVID-19 antibody status was checked; the test revealed the presence of COVID-19 antibodies in her blood. The proposed diagnosis of polyserositis likely triggered by a preceding viral infection was made, and a trial of colchicine was started.

OUTCOME AND FOLLOW-UP

The diagnosis of postviral polyserositis deemed secondary to COVID-19 was the key in this patient's care, and she was followed up regularly by the rheumatology team as an outpatient. She was started on 500 μg of colchicine two times per day for 6 weeks, which improved her symptoms. However, on reducing the dose to once per day, she began to feel unwell again. Her recurrent fevers returned with temperatures above 38°C recorded and she developed left-sided pleuritic chest pain, with a corresponding rise in her CRP to 240 mg/L. This was in keeping with a flare of polyserositis. Colchicine was therefore increased to 500 μg three times per day until clinical improvement and then reduced to the previous dose of two times per day for a total of 4 months. Following this, her colchicine dose was weaned down further until it was finally stopped. She was reviewed after a further 3 months and had no recurrence of her symptoms, with her fevers, pericardial effusion and pleural

effusion all resolved. She has now been discharged from regular rheumatology follow-up.

DISCUSSION

Currently, there are no other cases published in medical literature that report on polyserositis considered to be triggered by COVID-19.

Serositis is the inflammation and effusion of the pericardium, pleura or peritoneum, while polyserositis describes the inflammation, with effusion, of more than one of these sites. Due to its relative rarity, there are no diagnostic criteria or guidelines for polyserositis; the diagnosis relies on recognition of the clinical presentation and subsequent investigation for the common precipitants.¹

There aetiology of polyserositis is wide, with more common causes encompassing autoimmune disorders (systemic lupus erythematosus and rheumatoid arthritis),^{2,3} infection (*Mycoplasma pneumoniae*, *Legionella pneumophila*, tuberculosis, coxsackievirus, Epstein-Barr virus, cytomegalovirus and Q fever),⁴ autoinflammatory conditions (familial Mediterranean fever)⁴ and malignancy.⁵ However, a large proportion of cases remain idiopathic.

There is a dearth of large-scale studies looking at the aetiology of undifferentiated polyserositis. Yet one recently published retrospective analysis of patients admitted with polyserositis over a 12-year period has a number of interesting findings.¹ Neoplasm was found to be the most common diagnosis, occurring in 30.4% of patients, followed by infectious and autoimmune causes. Furthermore, the type of serosal involvement indicated the aetiology; neoplasm was associated in those with a combination of pleural effusion and ascites, whereas all infectious precipitants led to patients suffering from a combination of pleural and pericardial effusions. However, over one-third of patients had idiopathic disease, with no specific cause found.

In the case of the patient in this report, she was treated for acute bacterial infections on a number of occasions with no sustained improvement. A full typical viral screen yielded no positive result, and malignancy was excluded by full-body PET-CT. We hypothesise that the marked autoinflammation that COVID-19 is known to cause, acting via a maladaptive immune response and abnormal cytokine or chemokine production,⁶ led to the polyserositis. Though this is a novel association, a previous case report in 2019 highlighted the potential that an undiscovered autoinflammatory syndrome resulted in the same diagnosis of polyserositis.⁷ Colchicine led to a rapid and significant improvement in symptoms in that case as it did in this case, lending further credence to this hypothesis.

COVID-19 is a new disease, and although there is now an excellent understanding of the various ways in which it presents,

Learning points

- ▶ To our knowledge, this is the first case described with polyserositis possibly triggered by SARS-CoV-2 infection.
- ▶ It is important to consider rarer diagnoses when patients do not respond to treatment or have medically unexplained symptoms. We recommend a complete workup for bacterial, tuberculosis and viral infections, for autoimmune diseases and to exclude malignancy.
- ▶ Following the pandemic and prevalence of SARS-CoV-2, polyserositis post COVID-19 should be considered in the differential diagnosis of those presenting in a similar way.

the known sequelae of the disease are still evolving. Polyserositis is a diagnosis that is not often at the forefront of the physician's mind but should be considered when patients present with recurrent thoracic or abdominal pain, associated with fevers and raised inflammatory markers. Given the prevalence of COVID-19 during the pandemic, we hope to raise awareness of this challenging diagnosis in relation to SARS-CoV-2 and encourage further studies into the proposed underlying autoinflammatory process.

Contributors TV and EH designed the case study. TV was the main author concerned with the data collection. EH analysed and interpreted the data of the case study. EH and SS drafted the article. All authors were involved in the critical revision of the article and approved the final version to be published.

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