Poliserositis: un desafío diagnóstico

Polyserositis: a diagnostic challenge

Sérgio Costa-Monteiro, Raquel M. Vieira, Sara P. Bravo, Jorge Henriques

Internal Medicine. Unidade Local de Saúde da Região de Aveiro. Aveiro (Portugal)

ABSTRACT

Polyserositis, the inflammation of multiple serous membranes, presents a diagnostic challenge with etiologies ranging from neoplasms and autoimmune diseases to infections. Many cases remain idiopathic.

We describe a 72-year-old woman presenting with cardiac tamponade and bilateral pleural effusion, confirmed as exudative. Extensive workup excluded neoplastic, infectious, and autoimmune causes, leaving a recent SARS-CoV-2 mRNA vaccination as the only significant factor. A vaccine-induced systemic inflammatory response was hypothesized, with full recovery achieved using anti-inflammatory therapy.

This case highlights diagnostic complexity in polyserositis and suggests a rare potential adverse effect of mRNA vaccination.

Keywords: Systemic inflammatory response, mRNA vaccine, polyserositis.

RESUMEN

La poliserositis, inflamación de múltiples membranas serosas, representa un desafío diagnóstico con etiologías que van desde neoplasias y enfermedades autoinmunes hasta infecciones. Muchos casos permanecen como idiopáticos.

Describimos el caso de una mujer de 72 años que presentó taponamiento cardíaco y derrame pleural bilateral, confirmado como exudativo. Un exhaustivo estudio diagnóstico excluyó causas neoplásicas, infecciosas y autoinmunes, dejando como único factor significativo una reciente vacunación con ARNm contra el SARS-CoV-2. Se hipotetizó una respuesta inflamatoria sistémica inducida por la vacuna, con recuperación total mediante tratamiento antiinflamatorio.

Este caso resalta la complejidad diagnóstica de la poliserositis y sugiere un raro efecto adverso potencial de la vacunación con ARNm.

Palabras clave: Respuesta inflamatoria sistémica, vacuna de ARNm, poliserositis.

INTRODUCTION

Polyserositis, defined as the concurrent inflammation of multiple serous membranes (pleura, pericardium, peritoneum), is a rare condition often presenting with exudative effusions[1,2]. Its diagnosis is challenging due to nonspecific clinical manifestations and diverse etiologies, including neoplasms, autoimmune disorders, and infections. In some cases, no cause is identified, leading to an idiopathic classification[1,2]. Recent reports suggest that vaccines, including mRNA-based COVID-19 vaccines, may trigger systemic inflammatory responses resembling autoinflammatory or autoimmune conditions[3-7]. This report aims to contribute to this emerging body of knowledge by detailing a rare case of vaccine-associated polyserositis.

CLINICAL CASE

We present the case of a 72-year-old woman with no significant past medical history, who presented to the emergency department with a 3-day history of left pleuritic chest pain radiating to the shoulder, along with dyspnea on minimal exertion. She reported a 5 kg weight loss in the past month but denied fever, night sweats, gastrointestinal symptoms, or signs and symptoms of infection. Physical examination revealed dehydration, no fever, low blood pressure (99/55 mmHg), and diminished heart and breath sounds.

Initial laboratory tests show mild anemia, normal leukocyte count and low grade of inflammation. The complete initial laboratory tests, including autoimmunity and virology, showed no other specific changes and they are summarized in Table 1. Electrocardiogram (ECG) revealed low voltage QRS complexes without electrical alternans. A chest X-ray showed an enlarged cardiothoracic ratio and bilateral pleural effusions (Figure 1). An echocardiogram demonstrated a severe circumferential pericardial effusion causing right heart chamber collapse, consistent with cardiac tamponade. An emergent pericardiocentesis was been done, draining 110 mL of serohematic fluid. Post-procedure echocardiogram confirmed residual pericardial effusion.

In acute phase, a treatment with colchicine at 0.5 mg three times daily, ibuprofen 600 mg twice and prednisolone 40 mg once daily were initiated. Given the absence of evidence of an ative infection, it was decided not initiate empirical antibiotic therapy. The patient was hospitalized for further diagnostic workup, which included:

- SARS-CoV-2 RT-PCR: Negative.
- Serial blood cultures: Negative.
- Mycobacterial cultures (blood and pleural and pericardial fluids): Negative.
- Urine: Negative urine culture; BK-direct and BK-PCR negative.
- Fecal analysis: Negative coproculture. Negative fecal calprotectin. Negative parasitological analysis.
- Body CT scan: Pericardial and bilateral pleural effusion without other notable findings (Figure 2).
- Upper digestive endoscopy and colonoscopy: Normal.
- Mammography, breast ultrasound, and thyroid ultrasound: Normal.
- FDG-PET scan: No hyperfixation detected.
- Bronchoscopy: Normal findings.
- Bone marrow biopsy and myelogram: Normocellular marrow, with no changes in lineages and no signs of involvement by lymphocyte or plasma cell neoplasia. Negative myeloculture.

Correspondencia: 71258@chbv.min-saude.pt

Cómo citar este artículo: Costa-Monteiro S, Vieira RM, Bravo SP, Henriques J. Polyserositis: a diagnostic challenge. Galicia Clin 2025; 86-4: 15-19.
Recibido: 14/09/2024 ; Aceptado: 01/01/2025 // https://doi.org/10.22546/86/4/1350

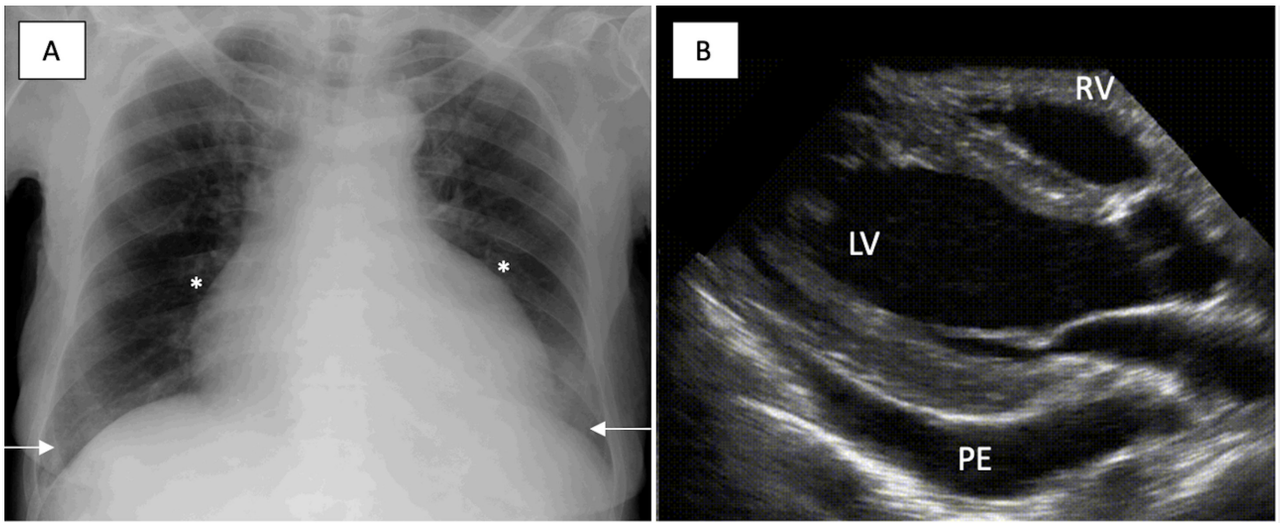


Figure 1. A. Chest X-ray at admission. Increased cardiothoracic ratio (asterisks) and bilateral pleural effusion (white arrows). B. Transthoracic echocardiogram at admission. PE – Pericardial effusion. LV – Left ventricle. RV – Right ventricle.

- Pericardial fluid analysis: 3000 cells with 60% neutrophils and 40% lymphocytes. Negative culture. ADA negative, with BK-direct and BK-PCR negative. Cytological with inflammatory aspects, predominance of neutrophils. Absence of neoplastic cells.
- Pleural fluid analysis: 238 cells with 14% neutrophils and 3% lymphocytes. Negative culture. ADA negative. BK-direct and BK-PCR negative. Cytological with reactive mesothelial cells, aspects suggestive of a reactive inflammatory process, with histiocytes and lymphocytes. Absence of neoplastic cells.
- Bronchoalveolar lavage and respiratory panel (*Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Bordetella pertussis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*): Negative for infections and neoplastic cells.

Both effusions were classified as exudates by Light's criteria, with inflammatory profiles. Cytological examination confirmed reactive mesothelial cells without neoplastic features. After ruling out neoplastic, autoimmune, and infectious causes, the recent administration of an mRNA SARS-CoV-2 vaccine 28 days prior was the only significant finding in the patient's history. It was hypothesized that the patient's polyserositis was triggered by a systemic inflammatory response to this mRNA vaccine, due this temporal association.

Inflammatory markers improved within a few days of anti-inflammatory treatment that included colchicine at 0.5 mg three times daily, ibuprofen 600 mg twice daily during two weeks and prednisolone 40 mg once a day during first 10 days, follow by three weeks of tapering regime. She was discharged after 30 days of hospitalization. An echocardiogram at discharge showed no significant pericardial effusion, and chest ultrasound confirmed resolution of pleural effusions. Laboratory tests at discharge are discriminated in Table 1.

The patient was discharged on a regimen of colchicine 0.5 mg twice daily during three months, with folic acid and vitamin D supplements. Six months later, she remained asymptomatic, with weight gain and no recurrence of symptoms or sequelae. Follow-up echocardiogram and chest X-ray were normal (Figure 3), and laboratory tests remained stable (Table 1).

DISCUSSION

Polyserositis remains an underdiagnosed condition, likely due to its nonspecific symptoms and overlapping features with other diseases. This case emphasizes the need for clear diagnostic criteria and further prospective studies to better understand its etiology and prevalence, as many cases are ultimately labeled idiopathic.[1,2]

Serositis might be attributed to numerous etiologies including infection, malignancy, uremia, or autoimmune disease[1]. In this patient, an exhaustive diagnostic workup excluded common causes such as neoplasia, infections, and autoimmune diseases. Pericardial effusion and pleural effusion were lymphocytes-predominant exudates and polymorphonuclear leukocytes could be yielded from them, serving as evidence of local inflammation of the pericardium and the pleura.

Neoplastic processes are a frequent cause of polyserositis, particularly lymphomas and metastatic tumors, which can invade serous membranes or induce secondary inflammatory effusions[1,2]. This was ruled out based on imaging, PET scan, and cytological analyses of all effusions, that didn't yield any malignant cell.

Infectious diseases (such as viral or bacterial infections) were also excluded. Viral infections, such as SARS-CoV-2, Epstein-Barr virus, and cytomegalovirus, can induce inflammation of serous membranes[1,2,5]. The normal white blood cell count, low level of C-reactive protein, negative procalcitonin value and all relevant cultures and serologies were all negative, made a primary infectious etiology less likely. High adenosine deaminase (ADA) levels in pleural or pericardial fluid are highly suggestive of tuberculous serositis. In this case, ADA levels were normal, and tuberculosis was excluded by negative PCR and culture results, further narrowing the differential diagnosis.

Autoimmune diseases, another key etiology, are commonly linked to systemic serositis, as seen in conditions like systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome. The patient had no family history or past history of an autoimmune disease, and lacked clinical and laboratory evidence of autoimmune diseases. Autoimmune polyserositis is often associated with elevated markers such as antinuclear antibodies, anti-double stranded DNA antibodies,

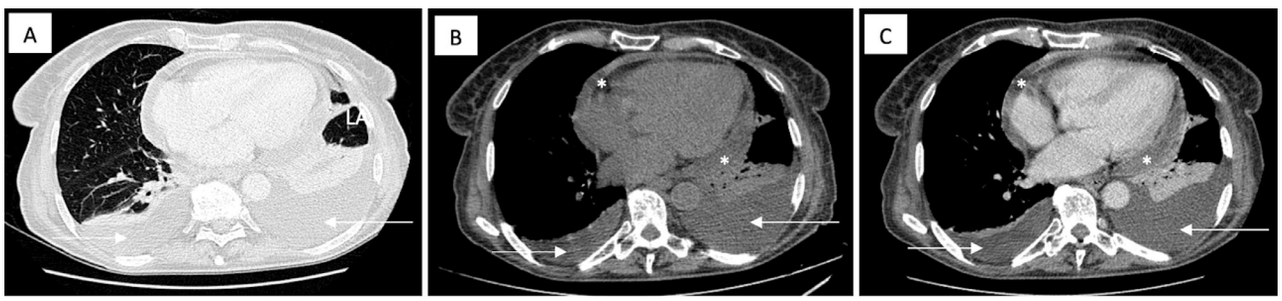


Figure 2. Body CT-Scan (A – Lung window. B – Without contrast. C – With contrast).
Asterisks - Circular pericardial effusion. White arrows - Bilateral pleural effusion.

or anti-SSA/SSB antibodies, none of which were present in this case. Finally, she had no typical presentation of any autoimmune diseases such as skin rash, muscle weakness, skin thickening, telangiectasia, oral ulcer, arthralgia, or Raynaud's phenomenon, so anyone autoimmune condition could be diagnosed with current criteria.

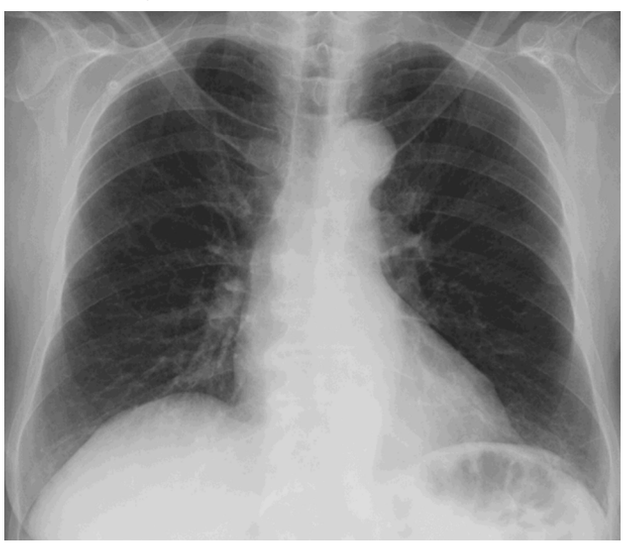
Thyroid function was normal, ruling out hypothyroidism. N-Terminal Pro–B-Type Natriuretic Peptide values are normal and congestive heart failure effusion usually is classified as a transudate, making the heart failure related serositis improbable. Finally, urea values are normal, so uremic serositis don't explained the clinical findings.

Idiopathic cases of serositis are common but reflect limitations in understanding its underlying mechanisms. The temporal association between symptom onset and mRNA SARS-CoV-2 vaccination strongly suggests a vaccine-induced inflammatory response. While these vaccines have shown high efficacy and safety profiles, some individuals develop autoimmune or autoinflammatory reactions post-vaccination. Several mechanisms have been proposed to explain post-vaccination inflammation of serous membranes, though none are fully understood. Proposed mechanisms include:

The temporal association between symptom onset and the recent administration of the SARS-CoV-2 mRNA vaccine strongly suggests a vaccine-induced inflammatory response as the most plausible explanation. Vaccines, including those for SARS-CoV-2, are known to trigger immune responses, and proposed mechanisms for this include hyperactivation of the immune system, cytokine overexpression, and molecular mimicry[5]. The robust immune response elicited by mRNA vaccines may cross-react with host proteins, leading to localized or systemic inflammation[3,5]. Additionally, lipid nanoparticles used in the formulation may activate the NLRP3 inflammasome, promoting the overproduction of pro-inflammatory cytokines like IL-1β[3,5]. Molecular mimicry may also play a role, with vaccine-induced antibodies targeting host antigens and triggering serosal inflammation[3,5]. Although these mechanisms remain hypothetical, similar inflammatory responses have been documented in isolated cases of polyserositis associated with vaccines, including those for SARS-CoV-2[3-5]. Although rare, vaccine-associated polyserositis has been described in isolated cases, supporting the hypothesis of immune dysregulation.[5]

Treatment in this case followed standard protocols and involves anti-inflammatory agents, such as colchicine, nonsteroidal anti-inflammatory drugs, and corticosteroids, which were effective in this case[8]. As proposed mechanisms for serositis induced by mRNA vaccine involves a disproportionate and uncontrolled activation of the inflammasome, with IL-1β-driven inflammation, some patients can develop

Figure 3. Chest X-ray at six months follow-up.
Absence of pleural effusion and normal cardiothoracic ratio.



recurrent polyserositis similar to those observed in some auto-inflammatory diseases, like Familiar Mediterranean Fever. In that cases, conventional anti-inflammatory therapies could be not able to control the disease and prevent relapses, so is important to consider optimized therapeutics like IL-1 inhibitors (anankira or canakinumab) that are effective agents in cases of persistent or severe polyserositis. Immunosuppressants can also be considered if autoimmune manifestations occur, like azathioprine or human immunoglobulin.[8]

It is important to say that there may be an association between COVID-19 vaccination and autoimmune and inflammatory diseases. Some autoimmune disorders seem to be more common than others and vaccines and SARS-CoV-2 may induce autoimmunity through similar mechanisms[6,9]. The most common diseases associated with new onset events following vaccination were immune thrombocytopenia, myocarditis, and Guillain-Barré syndrome. In contrast, immune thrombocytopenia, psoriasis, IgA nephropathy, and systemic lupus erythematosus were the most common illnesses associated with relapsing episodes.[5]

Polyserositis has also been linked to other vaccines, including pneumococcal and influenza vaccines. With the rollout of COVID-19 vaccination, various adverse effects have been reported, including myocarditis and pericarditis. These, while rare, are more commonly observed in younger males shortly after vaccination. Our literature search revealed only two cases of polyserositis associated with SARS-

Table 1. Analytical study at hospital admission, at discharge date and at 6 month-follow up after hospital discharge

	At admission	At discharge	At 6 month-follow up
Hemoglobin (g/dL)	11,4	11,0	12,9
Mean corpuscular volume (fL)	94,7	92,4	93,7
Mean corpuscular hemoglobin concentration (g/dL)	34,3	33,4	34,2
Leucogram	Normal	Normal	Normal
Platelets (x10^9/L)	392	342	301
Sedimentation rate (mm)	102	42	6
International Normalized Ratio	1,2	1,1	1,0
Urea (mg/dL)	18,9	41,1	51,4
Creatinine (mg/dL)	0,75	0,82	0,56
Ionogram	Normal	Normal	Normal
High-sensitivity troponin	Negative	-	-
Angiotensin converting enzyme (U/L)	59,3	-	-
Aspartate/Alanine aminotransferases	16/14	23/20	37/22
Bilirrubin levels	Normal	Normal	Normal
Alkaline phosphatase	66	70	56
Gamma-glutamyl Transferase	13	12	10
C-reactive protein (mg/dL)	6,7	1,9	0,23
Thyroid stimulating hormone (mU/L)	1,85	-	1,87
Albumine	3,7	3,5	3,9
Protein electrophoresis	Policlonality	-	Normal
N-terminal pro B-type natriuretic peptide (pg/mL)	931	123	89
Ferritin (ng/mL)	441	-	67
Folic acid (ng/ml)	2,09	-	5,4
Cianocobalamin (pg/mL)	416	-	567
Immunoglobulin A (mg/dL)	166	-	-
Immunoglobulin G (mg/dL)	822	-	-
Immunoglobulin M (mg/dL)	89	-	-
Complement levels (C3, C4)	Normal	-	Normal
Beta-2 Microglobulin (ng/mL)	2410	-	-
Alpha-1 Antitrypsin (mg/dL)	298	-	-
Rheumatoid factor	Negative	-	Negative
Anti-cyclic citrullinated peptide	Negative	-	Negative
Anti-double stranded DNA antibodies - IFI	Negative	-	Negative
Anti-nuclear and anti-cytoplasmatic antibodies - IFI	Negative	-	Negative
Toxoplasmosis IgG e IgM	Negative/Negative	-	-
Rubella IgG/IgM	Positive/Negative	-	-
Cytomegalovirus IgG/IgM	Positive/Negative	-	-
Epstein Barr IgG/IgM	Positive/Negative	-	-
Herpes Simplex 1 IgG/IgM	Positive/Negative	-	-
Herpes Simplex 2 IgG/IgM	Negative/Negative	-	-
Parvovirus IgG/IgM	Negative/Negative	-	-
Venereal Disease Research Laboratory (VDRL)/ Rapid Plasma Reagin (RPR)	Non reative	-	-
Human immunodeficiency virus	Negative	-	Negative

Hepatitis B virus antigen HBs	Negative	-	-
Hepatitis B virus antibody HBc	Negative	-	-
Hepatitis B virus antibody HBs	Positive	-	-
Hepatitis C virus Antibody	Negative	-	-
Hepatitrs A vírus IgG/IgM	Positive/Negative	-	-
Interferon Gama Release Assay	Negative	-	-
Urinalysis	Normal	-	Normal

CoV-2 mRNA vaccination: one, in a 65-year-old man; and another, in a 94-year-old-man[3,6,7]. However, we believe that this condition may be underreported or misdiagnosed, given its complexity and the difficulty in establishing a definitive etiology in many cases.

With this report, we illustrated the diagnostic challenges posed by polyserositis in clinical practice. The patient's age and clinical presentation would typically suggest more common causes such as neoplastic or autoimmune conditions, like lupus or rheumatoid arthritis, yet thorough investigation led to the exclusion of these. The temporal association between the onset of symptoms and vaccination, coupled with the exclusion of other causes, strongly supports vaccine-induced polyserositis as the most plausible diagnosis.

This case underscores the importance of considering recent vaccination in patients presenting with polyserositis, particularly when other causes have been excluded. While the association between vaccination and inflammatory responses is rare, its recognition is critical to guiding management. Further research is needed to elucidate the pathophysiological mechanisms of vaccine-induced inflammation, to establish treatment algorithms and to identify individuals predisposed to such events. Despite this extremely rare adverse effect, the benefits of SARS-CoV-2 vaccination far outweigh the risks, given its proven efficacy in preventing severe COVID-19 disease.

REFERENCES

1. Losada I, González-Moreno J, Roda N, et al. Polyserositis: a diagnostic challenge. Internal Medicine Journal. 2018; 48:982- 987.
2. Stoichitoiu L, Lonescu G, Neatu I and Baicus C. Causes of Polyserosistis: A Systematic Review. Journal of Personalized Medicine. 2023; 13:834.
3. Korzeniowska K, Ciesslewicz A, Flotynnska A and Jablecka A. Polyserositis (pericarditis and bilateral pleural effusion) after COVID-19 mRNA vaccine. Hematology in Clinical Practice. 2022; 13:15-22.
4. Segal Y and Shoenfeld Y. Cell Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction. Cell Mol Immunol. 2018; 15:586–594.
5. Rodríguez Y, Rojas M, Beltrán S, et al. Autoimmune and autoinflammatory conditions after COVID-19 vaccination: New case reports and updated literature review. Journal of Autoimmunity. 2022; 132:102898.
6. Lee SJ, Park DW, Sohn JW, et al. Vaccine-Induced Multisystem Inflammatory Syndrome with Polyserositis Detected by FDG PET/CT. Clinical Nuclear Medicine. 2022; 47(5):397-398.
7. Li GY, Lee CC and Huang CC. Acute Polyserositis with Cardiac Tamponade and Bilateral Refractory Pleural Effusion after ChAdOx1 nCoV-19 Vaccination. Vaccines. 2022; 10(8):1286.
8. Conte C, Princi G, D'Amario D, et al. Incessant pericarditis following the second dose of SARS-CoV-2 mRNA vaccine successfully treated with anakinra: a case report. European Heart Journal of Case Reports. 2022; 13:6(9).
9. Ceci B, Buhagiar K and Gouder C. An unusual case of post-covid-19 polyserositis. Hippokratia. 2023; 27(1):29.

CONFLICT OF INTEREST
All authors declare that there are no conflicts of interest in carrying out this work.

SOURCE OF FUNDING
There were no external sources of funding for this article for any of the authors.

ETHICAL ASPECTS
The patient's written consent was obtained for publication of this case.