CASE REPORT

Molecular diagnosis of opportunistic pericardial infection in a patient treated with adalimumab: the role of next-generation sequencing

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SUMMARY

Biological immune-modulator drugs, especially inhibitors of tumor necrosis factor- α , are frequently encountered in modern clinical practice and opportunistic infections are therefore a common concern. Infective pericarditis has been described as a complication of these treatments with possible life-threatening consequences. In similar cases cultures may isolate multiple opportunistic bacteria from the pericardial fluid without specific identification of the responsible germ, representing a problem for targeted antibiotic therapy. We present a case of acute pericarditis evolving in pericardial constriction and cardiac tamponade in a patient treated with adalimumab for psoriatic arthritis overlapping with recurrent polychondritis. Next-generation sequencing allowed the identification of a common oral pathogen as the aetiological agent confirming its role in the identification of species that can be overlooked by common microbiological techniques.

BACKGROUND

Biological immune-modulator drugs, in particular inhibitors of tumor necrosis factor- α (TNF- α), are commonly used for the treatment of a wide range of rheumatic diseases.¹ On the other hand, there is evidence that these patients are prone to opportunistic infections and screening is recommended.^{1, 2} The main concerns arise from non-tuberculous mycobacteria, histoplasmosis, coccidiomycosis and listeriosis, although the combination of anti-TNF- α , methotrexate and corticosteroids has been showed to increase overall susceptibility to infections.³

Purulent pericarditis is a rare life-threatening condition, frequently requiring surgical management for the development of pericardial constriction. In western countries <5% of acute pericarditis is caused by bacterial pathogens.⁴ Yet, in some cases multiple microbial agents are isolated from the pericardial fluid without specific identification of the responsible germ and therefore blood cultures are not contributory.

Next-generation sequencing (NGS) can be useful for the identification of otherwise uncharacterised opportunistic infections, especially if there is no a priori suspected agent.⁵

CASE PRESENTATION

A 55-year-old man was admitted to our department for acute pericarditis. The patient was chronically treated with adalimumab and methotrexate for

psoriatic arthritis overlapping with recurrent polychondritis.

At admission the patient had fever up to 38°C with elevated C reactive protein (CRP) (157 mg/dL) and white cell count (WCC) (15 710/ μ L) and presented typical pericardial pain (sharp retro-sternal chest pain worsening in the supine position and with inspiration and improving with sitting upright and leaning forward) and ECG alterations (figure 1); blood pressure was 115/75 mm Hg, heart rate was 75 bpm and echocardiogram revealed just modest pericardial effusion.

INVESTIGATIONS

During the following 3 days the pericardial effusion progressively increased, rapidly evolving towards pericardial tamponade with clinical signs of haemodynamic impairment (hypotension refractory to fluids, worsening renal failure with creatinine up to 2.05 mg/dL and anasarctic state). The patient underwent therefore emergent pericardiocentesis with drainage of 800 mL of purulent fluid over the next 24 hours. Thoracic CT scan, obtained few hours later, confirmed the persistence of large pericardial effusion and a concomitant severe pericardial thickening was observed (figure 2). Empirical antibiotic therapy with levofloxacin and amikacin was started and pericardial fluid and blood specimens were sent to the Microbiology laboratory for the preparation of traditional cultures and NGS. Blood cultures were negative but pericardial fluid cultures were positive for *Bacteroides thetaiotaomicron* (BT) and antibiotic therapy was switched, according to antibiogram, to amoxicillin clavulanate and clindamycin with good clinical and laboratoristic (CRP 418->50 mg/dL; WCC 32 000->6700/ μ L) response. Research of *Mycobacterium tuberculosis* on pericardial fluid and HIV test were negative.

Surprisingly, NGS response was just weakly positive for BT whereas it was positive at high degree for *Porphyromonas gingivalis* (PG), a common oral commensal (figure 3). The pericardial catheter was left in situ up to the 10th day because of trivial fluid drainage and NGS was hence repeated after 10 days of full antibiotic therapy: BT was no more identifiable but levels of PG DNA despite being partially reduced were still significant.

TREATMENT

Clinical signs of heart failure concomitantly persisted. Therefore, given the echocardiographic

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Figure 1 ECG at presentation showing diffuse ST segment elevation and PR segment depression.

(figure 4) and radiological evidence of pericardial constriction, the patient underwent surgical pericardial decortication (figures 5 and 6). Cultures of surgical specimens were negative for *M. tuberculosis* and anaerobic bacteria.

OUTCOME AND FOLLOW-UP

After a congruous prosecution of antibiotic therapy and physical rehabilitation the patient was discharged afebrile, in good haemodynamic compensation. One year after hospital discharge the patient is still asymptomatic from the cardiovascular point of view.

DISCUSSION

In developed countries purulent pericarditis is mostly a complication of previous pericardial diseases (uraemic, neoplastic or secondary to connective tissue diseases) or it is favoured by immunosuppression. The latter can be part of a systemic

condition (haematological disorders, chronic liver or kidney disease, alcoholism) or can be drug related.⁶

Data from registries of patients treated with anti-TNF- α drugs for rheumatic disorders reported an increased risk of bacterial infections, attributable to treatment and predisposing conditions such as more advanced or active rheumatic disease and higher burden of comorbidities.^{2 7}

To the best of our knowledge two cases of infective purulent pericarditis were previously described in patients treated with antirheumatic drugs. In one of these cases the aetiological agent was a common commensal (table 1).^{8 9}

Figure 2 Coronal CT scan reconstruction showing uniform pericardial hyperaemia and thickening without calcification and pericardial effusion (22 mm) just before the initiation of antibiotic therapy.

Species	Pericardial fluid before antibiotic therapy	Pericardial fluid after antibiotic therapy
<i>Porphyromonas gingivalis</i>	84%	59%
<i>Fusobacterium nucleatum</i>	8%	17%
<i>Peptostreptococcus anaerobius</i>	3%	10%
<i>Bacteroides ovatus</i>	2%	
<i>Dialister pneumosintes</i>	1%	1%
<i>Bacteroides thetaiotamicron</i>	1%	
<i>Treponema vincentii</i>	1%	2%
<i>Erysipelothrix rhusiopathiae</i>		2%
<i>Pseudomonas migulae</i>		1%
<i>Pseudomonas sp. QD03</i>		1%
<i>Elizabethkingia meningoseptica</i>		1%
<i>Treponema denticola</i>		1%
<i>Eubacterium sapenum</i>		1%

Figure 3 Ion Torrent Sequencing. The pooled library was diluted at a concentration of 26 pmo/L. Template preparation was performed using the Ion PGM Template OT2 200 kit on Ion OneTouch 2 System (Life Technologies, Grand Island, New York, USA), after which the enrichment percentage was carried out on Qubit 2.0 Fluorometer. The templates were sequenced on the Ion PGM System machine, using the Ion PGM sequencing 200 KIT V2 (Life Technologies, New York, USA). Readings were analysed using the MG-RAST server. The readings were grouped according to the taxonomic membership.

Figure 4 (A) Apical four-chamber view showing pericardial thickening with modest residual pericardial effusion; (B) dilated vena cava; (C) increased respiratory variation in early diastolic flow; (D) increased respiratory variation of hepatic venous flow. esp, expiration; insp, inspiration.

Figure 5 Intraoperative picture showing pericardial thickening.

Figure 6 Azan-Mallory stain of the pericardium showing multifocal phenomena of chronic inflammation with significant presence of fibroblasts.

PG is a Gram-negative, anaerobic pathogenic bacterium which belongs to oral microbiome and is involved in aggressive periodontal disease, a pathology frequently encountered in patients with rheumatic disease.¹⁰ Coinfection with *Fusobacterium nucleatum* can enhance the pathogenicity of PG by allowing the invasion of gingival epithelial cells.¹¹ In our case this mechanism was likely responsible of transitory bacteraemia and subsequent pericardial infection favoured by chronic immunosuppression. Traditional cultures could not correctly identify the pathogen, because of its specific culture conditions. In addition, BT infection was probably concomitant but not directly involved in pericarditis, given the persistence of purulent pericardial fluid despite negative cultures and NGS. This hypothesis is strengthened by the fact that PG can directly alter the immunological activating pattern determining further immunosuppression. Besides, the persistence of PG despite adequate antibiotic therapy is likely attributable to its ability to

Table 1 Similar published papers		
	Immunosuppressive drug	Pathogen involved
Lutman <i>et al</i> ⁹	Rituximab+methotrexate	Methicillin-sensitive <i>Staphylococcus aureus</i>
Taylor <i>et al</i> ⁸	Etanercept+methotrexate	<i>Peptostreptococcus micros</i>
Summary of previously published case reports on infective pericarditis during treatment with immunosuppressive antirheumatic drugs.		

escape antibiotic therapy infecting endothelial cells and producing a protective biofilm.¹² Finally, in this specific case, PG and BT were both sensible to the same drugs but this might not always be true; this aspect further highlights the importance of advanced microbiological

techniques such as NGS to achieve a correct diagnosis in similar life-threatening conditions.

To the best of our knowledge, this is the first case of opportunistic bacterial pericarditis in patients treated with adalimumab and the first reported employment of NGS for the analysis of pericardial fluid samples in a patient with bacterial pericarditis.

Learning points

- ▶ Prolonged treatment with adalimumab can pave the way to opportunistic infections.
- ▶ In patients treated with immune-modulator drugs presenting with acute pericarditis and pericardial effusion, opportunistic infection should always be suspected and carefully excluded.
- ▶ In case of constrictive pericarditis with severe and persistent haemodynamic impairment which cannot be controlled either by medical therapy or by pericardiocentesis, surgical pericardiectomy should be considered.
- ▶ Advanced microbiological techniques can be of great help to make an accurate aetiological diagnosis.
- ▶ Next-generation sequencing is a culture-independent method; thanks to the large number of samples that can be analysed at the same time it can provide useful information for the clinical practice at an affordable price; the cost-effectiveness is maintained even in the presence of multiple coinfections.

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conception and drafting of the manuscript; RL was involved in critical revision for important intellectual content; GS was involved in critical revision for important intellectual content and final approval of the version to be submitted. SP, MC (corresponding author) and GS agree to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved.

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