Recurrent non-infectious inflammatory endocarditis effectively treated with anakinra: a case report

Sirs,

We report a 33-year-old man with recurrent endocarditis that began in July 2022, complicated by aortic valve insufficiency in the absence of microbiological findings, necessitating biological valve replacement. In November 2023, the patient developed aortic valve stenosis and periprosthetic fluid collection, requiring new valve replacement surgery with mechanical aortic valve, closure of sub-valvular pseudoaneurysm, and simultaneous mitral valve repair for mitral insufficiency. In January 2024, he underwent a new aortic valve replacement with homograft prosthesis and mitral valve replacement with mechanical prosthesis due to recurrence of endocarditis. He also presented intermittent fever and increased inflammatory markers despite appropriate antibiotic therapy due to positivity at the 16S test for *Cutibacterium acnes* on valve material.

Laboratory findings at hospitalisation were significant for anaemia (Hb 8.7 g/dL), increase in C-reactive protein (CRP, 184 mg/L), serum amyloid A (SAA, 1,173 mg/L), and ferritin (1,043 ng/mL), while procalcitonin tested negative. Complete blood count did not show abnormalities, except a mild known neutropenia, previously investigated for immunodeficiencies and/or haematologic causes. Further testing included a comprehensive autoantibody panel (ANA, anti-ENA, anti-dsDNA, ANCA, anti-phospholipid antibodies, and rheumatoid factor), all of which resulted negative.

Although the patient did not fulfil the classification criteria for adult-onset Still's disease (AOSD) (absence of typical rash, lymphadenopathy, and leukocytosis) (1), high-spiking fever, inflammatory arthralgias, splenomegaly, and elevated inflammatory markers in the absence of infections were highly suggestive of an underlying systemic inflammatory process involving the cardiac valves.

Anakinra at a daily dose of 100 mg was started, with close clinical and laboratory monitoring. Within a week, the patient achieved a complete resolution of fever and arthralgias, with a consequent marked drop in inflammatory markers (CRP 6 mg/L, ferritin 597 ng/mL, SAA 35 mg/L) at 1 month. However, the clinical course was complicated by acute kidney failure (AKI) due to cardiogenic shock in progressive valvular degeneration and nosocomial polymicrobial sepsis with need of temporary anakinra discontinuation. After 2 months of hospitalisation (May 2024), he underwent mechanical Bentall surgery, hemiarch, and mitral valve replacement with mechanical prosthesis. Given the persistence of intermittent fever and rapidly increasing inflammatory markers, therapy with anakinra 100 mg/day was reintroduced, with marked clinical and laboratory improvement. The patient fully recovered 30 days after surgery and was discharged on daily subcutaneous anakinra. After 12 months, the patient still presents excellent general conditions with no signs of endocarditis recurrence. Anakinra was well tolerated without major adverse events, together with G-CSF administration periodically subcutaneously due to persistent mild leukopenia.

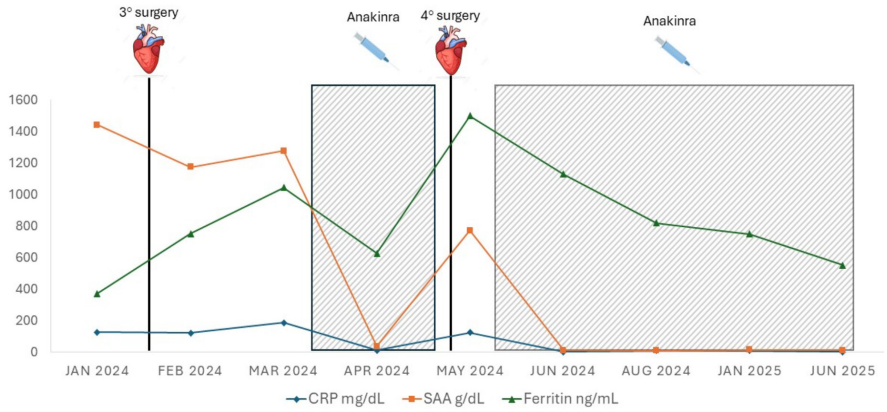

Fig. 1. Course of laboratory parameters at different time points before and after surgery and anakinra treatment. The dosage of subcutaneous anakinra was 100 mg/day.

Endocarditis rarely occurs in the context of systemic autoimmune disease (SAD), mainly systemic lupus erythematosus (SLE) and antiphospholipid syndrome, and is seldom described in AOSD (2-4) or in sporadic idiopathic cases (5).

Our patient developed intermittent fever approximately 10 days after receiving typhoid and yellow fever vaccinations, preceding the first episode of endocarditis. Vaccinations are recognised as potential triggers of SAD in predisposed individuals. Furthermore, the only microbiological finding was *Cutibacterium acnes* on the valve tissue, an organism rarely implicated in severe opportunistic infections, but capable of activating inflammasome and promoting IL-1β release in human neutrophils *in vitro* (6).

In our case, establishing a definitive diagnosis remains challenging, due to pre-existing conditions (such as baseline neutropenia), which complicate the distinction between an incomplete phenotype of AOSD or idiopathic non-infective endocarditis. Nevertheless, the systemic involvement exhibited by the patient, together with the predominant cardiac manifestations, suggest a clinical entity closely related to AOSD.

While the role of IL-1 in inflammatory pericarditis and myocarditis, as well as in AOSD pathogenesis, is well established (7), its involvement in non-infectious endocarditis remains largely unexplored. Interestingly, the IL-1 recombinant receptor antagonist (IL-1Ra) anakinra has shown efficacy in idiopathic pericarditis and myocarditis (8, 9), while, to the best of our knowledge, only one case-report on non-infectious inflammatory endocarditis successfully treated with anakinra has been reported (5). Notably, anakinra has been safely administered to critically ill patients with sepsis in intensive care settings (10), and current EULAR/PReS guidelines (11) recommend IL-1 blockade for the treatment of AOSD, even when bacterial infection remains part of the differential diagnosis.

In the present case, the incomplete features of AOSD, combined with the patient's progressive clinical instability and high surgical risk, posed significant therapeutic challenges requiring a careful risk-benefit assessment. A combined surgical and medical approach with anakinra preserved valvular tissue integrity by limiting further inflammatory damage.

In summary, we report a case of recurrent inflammatory endocarditis in a young man presenting with features resembling an atypical form of AOSD, requiring multiple cardiac surgeries. In the absence of identifiable infectious agents, inflammatory aetiologies should be carefully considered. However, further research is needed to evaluate the true efficacy and safety of anakinra in the treatment of non-infectious endocarditis, both in the context of AOSD and in idiopathic inflammatory cases.

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