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BMJ Case Reports

Full clinical cases submission template

TITLE OF CASE ***Do not include "a case report"***

Auto-inflammatory constrictive pericarditis and chronic myelomonocytic leukaemia (CMML). When one speciality is not enough.

SUMMARY ***Up to 150 words summarising the case presentation and outcome (this will be freely available online)***

We present a case of constrictive pericarditis with concomitant blood and bone marrow appearances of chronic myelomonocytic leukaemia (CMML). Despite surgical treatment with pericardiectomy, the patient deteriorated into multi-organ failure. Pericardial histology disclosed a typical-inflammatory picture with no evidence of monocytic or malignant infiltrate. Following intensive collaboration between cardiologists, haematologists and rheumatologists via daily email exchanges, a diagnosis was reached of autoinflammatory constrictive pericarditis with a non-infiltrative coexisting CMML. The key to achieving a rapid and sustained response was a trial of high dose steroids followed by intravenous immunoglobulins (IVIG). This achieved restoration of cardiac function, resolution of symptoms and near normalisation of inflammatory markers. A diagnosis of concurrent CMML was confirmed at 3 months. The patient remains well, taking colchicine and steroids.

BACKGROUND ***Why you think this case is important – why did you write it up?***

Less than one fifth of cases of pericarditis present with a specific aetiology.[1] This patient did not present typically for constriction; nor did he meet the criteria for acute or chronic myelomonocytic leukaemia.[Table 1][2] Weight loss and lack of response to standard treatment suggested there was likely to be a pathogenic underlying aetiology. Successful diagnosis and treatment was only achieved with daily cross-speciality input from haematology, cardiology and rheumatology. Consideration of early trial of high dose steroids in addition to combination therapies including a novel use of intravenous immunoglobulins (IVIG) led to complete recovery. This case highlights the need for rapid and decisive liaison between specialists (in this case via hospital email to minimise delays) in complex cases of acute constrictive auto-inflammatory pericarditis.

CASE PRESENTATION ***Presenting features, medical/social/family history***

An active, Caucasian male in his late 70s presented with a six week history of 10kg weight loss and epigastric pain radiating to the back. There was no dyspnoea, fever, sweating or recent illness. His past medical history included a left trigeminal nerve Schwannoma two years previously (successfully treated with gamma knife irradiation), peptic ulcer disease and

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hypertension. He was an ex-smoker with no significant alcohol or recreational drug history. On examination, vital signs were within normal range, he had a raised jugular venous pulse, basal crepitations and a pericardial friction rub. There was no palpable lymphadenopathy or hepatosplenomegaly. The ECG revealed left bundle branch block, widespread concave ST segment elevation and left axis deviation.

INVESTIGATIONS ***If relevant***

Chest radiography revealed clear lung fields with cardiomegaly. An echocardiogram showed moderate to severely impaired left ventricular function with an akinetic, thinned lateral myocardium and a thickened pericardium causing likely constriction but no effusion.[Fig 1.] Computed chest tomography confirmed a thickened pericardium.[Fig 2.] A coronary angiogram was performed which demonstrated normal coronary arteries making Dressler's syndrome unlikely though coronary embolus could not be entirely excluded. Full blood count revealed: Hb 103 (131-166), Plt 126 (150-400) and WBC 17.5 (3.5-9.5), monocytosis 8.75 (0.25-1.0) which was morphologically consistent with CMML but did not meet diagnostic criteria.[Table 1][2] Serum C-reactive protein level was 232 (<5) and Ferritin 812 (30-400). Serial High Sensitivity Troponin-T (HSTnT) were 25, 24, 27 (<14). A complete Viral PCR was performed from respiratory, stool and serological samples. This included: Human Immunodeficiency Virus (HIV), Hepatitis B and C, Ebstein Barr Virus (EBV), Cytomegalovirus (CMV), Influenza A/B, Parinfluenza 1-4, Human Metapneumo-, Rhino-, Corona-, Entero and Adenoviruses, Human Herpes Virus-6 (HHV6) and HHV7. The results were all negative. Bone marrow biopsy was morphologically consistent with CMML-1,[Fig 3] however the monocytosis has not yet persisted over 3 months and reactive monoclonal causes had not yet been excluded at the time.[Table 1][2] Immunophenotyping showed no increase in CD34+ myeloid blast cells with a mature monocytic component, expressing CD14 at 22%. Cytogenetics showed normal male karyotype. FISH analysis of 100 interphase nuclei has shown no evidence of BCR-ABL1 rearrangement nor evidence of Platelet Derived Growth Factor Receptor (PDGFR-A, PDGFR-B) or Fibroblast Growth Factor Receptor (FGFR-1) rearrangement at chromosomes 4q12, 5q32 and 8p11, respectively (99% chance of detecting a 5% cell population), and JAK-2 mutation was not detected. High throughput and Sanger sequencing was requested for somatic myeloid mutation analysis. A diagnosis of pericarditis with constrictive features due to a reactive monocytosis was considered. It was unclear whether this was secondary to infiltration or inflammation.

Table 1: Diagnostic criteria adapted from WHO (2016) CMML criteria.[2]

All FIVE of the following must be met:	
Peripheral Blood	Persistent monocytosis ≥1 × 10^9/L, with monocytes accounting for ≥10% of the WBC count and <20% blasts
Flourescence In Situ Hybridisation (FISH) analysis	No evidence of *PDGFR-A*, *PDGFR-B*, or *FGFR-1* rearrangement or *PCM1-JAK2* (to be specifically excluded if eosinophilia)
Bone Marrow	<20% blasts (including myeloblasts, monoblasts and promonocytes)
Exclusions	Not meeting WHO criteria for *BCR-ABL1* CML, PMF, PV, or ET as cases of myeloproliferative neoplasms (MPN) can be associated with monocytosis and simulate CMML. Presence of these features in the bone marrow or MPN-associated mutations (*JAK2*, *CALR*, or *MPL*) tend to support alternative diagnosis of MPN with monocytosis
Myelodysplasia	Present in one or more myeloid lineages. *However i*f absent or minimal and all other requirements are met can be diagnosed if an acquired clonal cytogenetic or molecular genetic abnormality is present *Or* the monocytosis has persisted for at least 3 months, *and* all other causes of monocytosis have been excluded (e.g. infection, inflammation, malignancy)
Subcategories	
CMML-1	< 5 % blasts (promonocytes, monoblasts, myeloblasts) in the blood and < 10% blasts in the marrow
CMML-2	5 – 19% blasts in the blood, OR 10 – 19% blasts in the marrow, OR presence of Auer rods

DIFFERENTIAL DIAGNOSIS *If relevant*

Initial presentation suggested dominant cardiac failure with constrictive pericarditis. Initial differentials considered myocardial aetiologies such as Takotsubo's cardiomyopathy or myocardial infarction however these were not explained by imaging or angiographic results. The aetiology of constrictive pericarditis in a previously fit, ex-smoking white male was unlikely to be tuberculosis (quantiferon gold testing was negative). There was no history of pre-existing auto-immune disease and virology was negative. Weight loss and marked monocytosis raised the possibility of an infiltrative leukaemia, but cytogenetic testing of the bone marrow biopsy and cytological examination of the pleural aspirate were negative by formal criteria. Monocytic infiltration of the pericardium was therefore thought to be unlikely, but was not yet excluded. The main differential was therefore a reactive macrophage activation syndrome secondary to acute pericarditis of undetermined aetiology. Pericardiectomy offered the opportunity to provide therapeutic and diagnostic benefit. Surgical options considered were Video-Assisted Thorascopic

Surgery (VATS) offering a smaller incision and biopsy versus midline sternotomy and pericardiectomy. The key determinant in approach was whether constriction was present, requiring left and right heart catheterisation.

TREATMENT ***If relevant***

Despite an adequate trial of colchicine, the patient's condition was deteriorating and serial CRP measurements remained high (150-300). By day 10 he worsened with cardiac, respiratory and renal failure and congestive liver injury. There was a pleural effusion, which was drained. Pleural fluid analysis revealed an exudate according to Light's criteria.[3][4][5] Left and right heart catheterisation disclosed elevation of right sided pressures with equalisation of the diastolic pressure throughout all cardiac chambers. In order to treat deterioration and achieve definitive diagnosis, a pericardiectomy was performed via midline sternotomyat day 19. This failed to deliver clinical benefit or a definitive diagnosis, but did exclude neoplasia, TB and infiltration. Histology was consistent with a pattern typical of a non-specific inflammatory process.

In the absence of infiltration, and with confirmation of an underlying inflammatory condition, prednisolone 60mg daily was commenced. This led to an improvement in CRP, but pleural effusions re-accumulated. The cardiac failure continued to be resistant to intravenous diuretics with no improvement in left ventricular function and the clinical picture deteriorated further.[Fig 4] Empirical trial of high dose methylprednisolone led to improvement in inflammatory markers, blood count and heart failure parameters.

This sustained improvement to high dose steroids suggested an inflammatory disorder either driven by, or driving, the monocytes, but cause and effect remained unclear. Further daily exchanges between the relevant specialties raised the possibility of an auto-inflammatory serositis. Treatment with IVIG was initiated. With this regimen he showed a further marked improvement in symptoms, physical signs and organ function. The patient was discharged from hospital 14 days later (13 weeks after admission).

OUTCOME AND FOLLOW-UP

Four months later, he remains well and has resumed normal activities. Maintenance therapy comprises reducing doses of prednisolone and colchicine. Left ventricular function had completely recovered by 8 weeks.[Fig 5] Follow-up over three months demonstrated persistence of the monocytosis despite resolution of his inflammatory disorder. High throughput and Sanger

sequencing also detected TET2, ASXL1 and SRSF2 mutations, thereby confirming clonality and a diagnosis of CMML-1.[Table 1][2] His current results show a CRP of 32 (<5), WCC 37.8 (3.5-9.5) and monocyte count of 13.57 (0.25-1.0). No active treatment is required for his CMML. The diagnostic conclusion drawn was a rare, life-threatening case of acute inflammatory carditis (involving both myocardium and pericardium). We conclude that this was triggered by underlying CMML.[6][7]

DISCUSSION ***Include a very brief review of similar published cases***

This case was an unusual presentation of both CMML and pericarditis with few typical features of either condition. There was no evidence of leukaemic infiltration in the pericardial histology. There was little initial response in LV function to pericardiectomy, and no resolution of monocytosis or CRP to colchicine but an encouraging response to high dose steroids and a definitive response to IVIG. Multi-disciplinary input, with rapid and frequent discussion was vital for reaching a unifying diagnosis and achieving therapeutic success.

Standard treatment for CMML varies depending on blood counts, severity of the bone marrow appearances, proliferative markers and corresponding prognostic scores.[8] Milder forms have a median life expectancy of greater than 8 years. These cases require 'watchful waiting' or 'active observation' in the outpatient setting with monitoring of full blood count parameters at regular intervals. Symptomatic treatment for common complications such as anaemia, infection or severe thrombocytopenia may be required. In this case, treatment was required for pericarditis. In cases of more advanced disease with high prognostic scores, active treatment options include hypomethylating agents, chemotherapy and allogenic stem cell transplantation.

This case also highlights the need for careful consideration of the differential diagnoses in acute pericarditis. In Western Europe, most cases are idiopathic (78-86%), the remainder being neoplastic (5-7%), tuberculous (4%) and autoimmune or post-cardiac surgery (1-7%).[1] The subset progressing to constriction in developed countries are idiopathic (33-46%), post-radiation (9-31%), post-surgery (11-37%), post-infective (4-20%) or due to connective tissue disease (3-7%).[1] Many undiagnosed aetiologies of carditis are likely to be viral in origin. These include, but not exclusively, HIV, EBV, CMV, influenza-, adeno-, entero- and herpes-viruses. Aside from HIV, routine screening is not recommended as this rarely impacts on treatment and is not cost-effective.[9] Pericarditis with a non-idiopathic aetiology are more likely to present with clinical markers such as high fever, subacute onset, large pericardial effusion, cardiac tamponade and lack

of response to aspirin or non-steroidal anti-inflammatory agent (NSAID).[1]

European Society of Cardiology Guidelines,[1] for the management of pericarditis recommend NSAIDs with proton-pump inhibitor (PPI) cover as first line treatment. Most treatment failures in acute pericarditis are due to inadequate treatment doses or interruption in course of treatment.[1] Whilst colchicine can reduce the recurrence in acute pericarditis by about 50%, this generally fails in monotherapy. Efficacy has been demonstrated for combination therapy with NSAID and in poorly responsive cases, corticosteroids. Azathioprine is useful as a steroid-sparing agent. In recurrent acute episodes, both IVIG and an interleukin-1 receptor antagonist (Anakinra) are recommended. This case demonstrated the novel incorporation of a biological agent in quadruple therapy for a first, but life-threatening, presentation of acute carditis. Guidelines advise continuation until complete resolution of symptoms and normalisation of the CRP are achieved.

LEARNING POINTS/TAKE HOME MESSAGES ***3 to 5 bullet points – this is a required field***

- The presence of both pancarditis and monocytosis should prompt a unifying aetiology such as an autoinflammatory disorder.
- Pericarditis presenting with a significant monocytosis should involve exclusion of malignant infiltration (haematological and non-haematological causes), infective, autoimmune and connective tissue diseases.
- Early use of more aggressive treatments (e.g. IVIG/Anakinra) in cases of autoimmune pericarditis showing immediate response to high dose prednisolone should be considered.
- Close multi-disciplinary input (daily email updates and discussions) may be required to effectively diagnose and treat complex cases such as this.

REFERENCES ***Vancouver style (Was the patient involved in a clinical trial? Please reference related articles)***

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FIGURE/VIDEO CAPTIONS ***figures should NOT be embedded in this document***

Fig 1. Admission echocardiography showing moderate to severe left ventricular impairment
Fig 2. Computed Tomography demonstrating thickened pericardium
Fig 3. Bone marrow aspirate appearance suggestive of CMML (x50)
Fig 4. Echocardiography pre- and post-pericardiectomy showing severe left ventricular impairment
Fig 5. Normal echocardiography 8 weeks post-discharge
Fig 6.

PATIENT'S PERSPECTIVE ***Optional but strongly encouraged – this has to be written by the patient or next of kin***

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