CASE REPORT

Hypereosinophilic syndrome associated with ulcerative colitis presenting with recurrent Loeffler's endocarditis and left ventricular thrombus treated successfully with immune suppressive therapy and anticoagulation

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SUMMARY

We reported a case of a 28-year-old Caucasian woman with hypereosinophilic syndrome (HES) associated with ulcerative colitis who presented on separate occasions with Loeffler's endocarditis. She was admitted in 2008 with fever, headache, confusion and visual loss. Diagnostic workup uncovered an eosinophilia of $3.1 \times 10^9/L$ and major ECG abnormalities. Subsequent echocardiography revealed left ventricular wall motion abnormalities with mural thrombus. MRI brain scan showed multiple white matter lesions consistent with acute infarcts. She recovered rapidly with corticosteroids and anticoagulation. Four years later she re-presented with headache, fatigue and an eosinophilia of $13.4 \times 10^9/L$. This occurred 3 months after cessation of immunosuppression and within 12 months of total colectomy for fulminant ulcerative colitis. Echocardiography was suggestive of hypereosinophilic endomyocardial fibrosis with left ventricular thrombus. Anticoagulation and corticosteroids were resumed with good effect. This report highlights the findings, treatment and outcome of ulcerative colitis-associated HES manifesting as recurrent Loeffler's endocarditis.

BACKGROUND

Hypereosinophilic syndrome (HES) is a group of disorders characterised by overproduction of eosinophils, with eosinophilic infiltration causing multi-organ damage. HES incidence was noted to be between 0.018 and 0.036/100 000 person-years. HES is defined by blood eosinophilia of greater than $1.5 \times 10^9/L$ (> 1500 eosinophils/ mm^3), present on at least two occasions 6 months apart with no other apparent aetiology for this degree of eosinophilia. This case report describes the associated HES, a variant of HES, with cardiac involvement and underlying ulcerative colitis.

CASE PRESENTATION

In 2008 a then 24-year-old woman presented to the emergency department with a 3-day history of severe headache associated with subjective fevers, chills, arthralgia, nausea and blurred vision. Her husband also described fluctuating orientation with an inability to perform usual household tasks. This was on a background of longstanding ulcerative colitis requiring immunosuppression, mild sclerosing cholangitis and a deep venous

thrombosis occurring post-appendectomy in childhood. She also had a history of migraine.

On examination she was lying with her eyes closed, moaning and hyperventilating. On eye opening she was found to not be fixing gaze and vision was reduced to detecting light only. She had fluent speech but was agitated and not able to follow two-stage commands. After the initial investigation she was treated empirically with antibiotics, aciclovir and dexamethasone for probable meningoencephalitis.

Further investigation found no evidence of infection, but was suggestive of myocarditis, left ventricular thrombus, and multiple acute cerebral infarcts. Antimicrobials were ceased after several days and she was discharged on corticosteroids and anticoagulation. Apart from a mild residual left-sided visual field deficit she made a complete recovery.

Four years later she presented with increased headaches, fatigue, dizziness and vague constitutional symptoms. During the previous 12 months she had experienced severe ulcerative colitis that ultimately required treatment by urgent colectomy. A distal rectal stump remained. Her immunosuppression, which at different times had included prednisolone, azathioprine, 6-mercaptopurine (6-MP) and infliximab, had been ceased 3 months prior to this presentation. She was diagnosed and treated for migraine with incomplete symptomatic relief, and further investigations were undertaken.

INVESTIGATIONS

During the initial presentation in 2008 laboratory investigation confirmed a systemic inflammatory illness with C reactive protein 174, white cell count $15 \times 10^9/L$ with toxic neutrophilia and eosinophilia of $3.1 \times 10^9/L$. A vasculitic screen was positive for p-antineutrophil cytoplasmic antibody (ANCA). Lumbar puncture was normal. Blood, urine and cerebrospinal fluid cultures were negative. Contrast CT of the brain showed small irregular focal areas of hypodensity in the subcortical white matter with a 10 mm $\times$ 9 mm lesion in the region of the right frontal lobe that had ring enhancement. MRI of the brain revealed lesions in the white matter of both parieto-occipital lobes that were hyperintense on T2-fluid-attenuated inversion recovery and hypointense on T1-weighting, consistent with acute infarcts. Global T-wave inversion was evident on ECG. On

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echocardiography (ECHO) there was a mildly dilated left ventricle with mildly hypokinetic apical walls with overlying 1 cm thick mural thrombus (figure 1 and video 1). There was also a small pericardial effusion.

At re-presentation 4 years later the ECG, which had normalised after previous anticoagulation and left ventricular thrombus resolution, was found to once again be abnormal. Troponin I was elevated at 2.1 µg/L. Her white cell count was $27.3 \times 10^9/L$ with a marked eosinophilia of $13.4 \times 10^9/L$. Echocardiography showed typical features of hypereosinophilic endomyocardial fibrosis with left ventricular apical thrombus (figure 2 and video 2). Such a pattern is often described in Loeffler's endocarditis. This was confirmed with cardiac MRI (figure 3 and video 3). Repeat MRI of the brain noted only old infarcts.

During haematological consultation she was evaluated for the presence of inherited or acquired thrombophilic disorders. These were excluded. Bone marrow biopsy showed no evidence of a myeloproliferative disorder. C-Kit mutation or BCR-ABL gene were not detected in the marrow sample. Karyotype and immunophenotype were normal. Furthermore FIP1L1-PDGFR fusion gene or C-Kit gene mutation with D816 V substitution were not detected.

DIFFERENTIAL DIAGNOSIS

At initial presentation the patient was thought to have myocarditis and probably vasculitis associated with ulcerative colitis. The cardiac and apparent central nervous system (CNS) involvement, along with eosinophilia and positive p-ANCA raised the possibility of Churg Strauss vasculitis. Malignant causes of HES such as chronic or acute eosinophilic leukaemia or myeloproliferative disorder were excluded.

TREATMENT

At the initial presentation in 2008 the patient was started on high-dose prednisolone for vasculitis and enoxaparin for the left ventricular thrombus and cerebral infarcts. Her repeat echocardiography performed 6 months later while on prednisolone at a daily dose of 15 mg and warfarin showed complete resolution of the left ventricular thrombus with normal systolic function and no regional wall motion abnormalities. She remained on long-term immunosuppression for ulcerative colitis and the warfarin was later changed to aspirin.

Figure 1 Transthoracic echocardiography showing four-chamber view of the left and right ventricles with (lower arrow) highly echogenic organised apical thrombus in the left ventricular cavity along with thickening of the apical segments of left ventricle (upper arrow).

Video 1 Transthoracic apical four chamber view depicting highly echogenic mass obliterating left ventricular apex.

At re-presentation 4 years later the patient had been off-immunosuppressant treatment for 3 months. This followed urgent colectomy earlier in the year for fulminant ulcerative colitis. During this second presentation, Loeffler's endocarditis as a manifestation of HES was diagnosed. She was once again treated with high-dose oral corticosteroids and anticoagulation to good effect. 6-MP was started as the steroid sparing agent of choice, given the patient's previous tolerance of this medication, its proven-role in the treatment of ulcerative colitis and the absence of HES while the patient was on it.

OUTCOME AND FOLLOW-UP

The patient's symptoms resolved within days of starting prednisolone and warfarin. Her eosinophil count normalised within 4 weeks and repeat echocardiography after 5 months has shown significant improvement of left ventricular function along with significant resolution of apical mural thrombus (figure 4 and video 4). We are aiming to taper her prednisolone dose and continue with 6-MP at least for as long as the rectal stump remains in situ. There are plans for further surgery and it remains to be seen whether the hypereosinophilia will resolve with resection

Figure 2 Colour Doppler flow showing diastolic (red) and systolic (blue) flow of blood over the echogenic mass in the four-chamber view.

Video 2 Colour flow doppler imaging of left ventricle demonstrating intracavitary flow and obliterated apex.

Video 3 Cardiac MRI sequence with apical four chamber view showing a large mural thrombus filling the left ventricular cavity with no right ventricular involvement.

of the last of the patient's bowel. She continues on long-term anticoagulation. She will continue to have clinical follow-up and echocardiography every 6 months.

DISCUSSION

HES is a rare condition marked by the sustained overproduction of eosinophils. It is often, but not invariably, associated with damage to multiple organs due to eosinophilic infiltration. Cardiac signs and symptoms are only seen in 5% of cases.¹ Patients are usually diagnosed between the ages of 20 and 50 years.² Eosinophilic myocarditis is a major cause of morbidity and mortality among patients with HES.¹⁻³ HES may have lethal complications including endomyocardial fibrosis and neurological involvement.

Eosinophil-mediated heart damage evolves through three stages: it starts with an acute necrotic stage followed by an intermediate phase, which is characterised by thrombus formation and endocardial damage. It ends with a fibrotic stage.²

The initial necrotic phase is usually clinically silent and is characterised pathologically by endocardial damage, myocardial infiltration with eosinophils and lymphocytes, eosinophil degranulation, myocardial necrosis and the formation of sterile microabscesses. Elevations in serum troponin levels can be a sensitive indicator of early and ongoing eosinophil-associated myocardial damage.⁴⁻⁶

Contrast-enhanced cardiac MRI reliably detects all stages of eosinophil-mediated heart damage, including the early stage of myocardial eosinophilic inflammation.⁷⁻⁸ Echocardiography can be normal during the acute necrotic stage. Echocardiography and cardiac MRI⁹ may demonstrate intracardiac thrombi during the second stage of disease involving thrombus formation along areas of damaged endocardium. Endomyocardial biopsy may provide definitive evidence of eosinophil-associated cardiac involvement and is reserved for patients with diagnostic uncertainty.

Figure 3 Cardiac MRI sequence through the four-chamber view showing large mural thrombus (upper arrow) in the left ventricular apex (middle arrow) without any right ventricular involvement (lower arrow).

Figure 4 Standard apical four-chamber view taken after 5 months of treatment, showing left ventricular cavity (arrow) free of thrombus with preserved apical wall contractility.

Video 4 Transthoracic echocardiography repeated after 5 months showing significant resolution of left ventricular thrombus with well preserved left ventricular systolic function.

In the final fibrotic stage, progressive scarring causes endomyocardial fibrosis, producing a restrictive cardiomyopathy and valvular regurgitation due to entrapment of the chordae tendineae. An echocardiography and a cardiac MRI may show evidence of fibrosis.

Our patient has evidence of endomyocardial fibrosis with mural thrombus due to Loeffler's endocarditis. However, she has maintained adequate left ventricular function and has normal heart valves. She has a mild visual field deficit due to an associated stroke.

The nature of the CNS disease at initial presentation remains undefined. Cerebritis, which is more typically associated with systemic lupus erythematosus, may be seen on CT scanning as an ill-defined low-density area with peripheral enhancement, as seen in this case. Cerebral vasculitis has been reported in patients with ulcerative colitis.¹⁰ Eosinophils may penetrate the CNS and cause disease directly in HES. The cerebral infarcts seen on MRI were thought to be due to embolism from the left ventricular thrombus.

In summary, we presented a case of HES in association with ulcerative colitis that presented on separate occasions with Loeffler's endocarditis.

Learning points

- ▶ A rare acquired hypereosinophilic syndrome (HES) with classical Loeffler's endocarditis complicated by cerebral infarction was treated successfully with anticoagulation and corticosteroid therapy.
- ▶ Our case study demonstrates that patients with cardiac involvement require ongoing anticoagulation and immunosuppressive treatment.
- ▶ This case report highlights the association of ulcerative colitis with HES and the occurrence of the potentially lethal complication of recurrent Loeffler's endocarditis.

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Contributors SK collected the data, KG, SC and KAA were involved in the treatment of this complex case. All contributed in writing and editing and finally approved the manuscript.

Competing interests None.

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