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CASE REPORT
Other

Heart valve disease in hypocomplementemic urticarial vasculitis syndrome: from immune-mediated degeneration to embolic complications of infective endocarditis—a case report

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Background Hypocomplementemic urticarial vasculitis syndrome (HUVS) is a rare disease due to small vessel inflammation and characterized by chronic urticarial vasculitis and arthritis. Multi-organ manifestations may include glomerulonephritis, ocular inflammation (uveitis, episcleritis), and recurrent abdominal pain. To the best of our knowledge, just other nine cases of HUVS with cardiac valvular involvement have been reported in the literature.

Case summary A 32-year-old woman presented to the emergency department because of a cerebral haemorrhage. She suffered from a severe HUVS form with cardiac valvular involvement. In the previous years, she underwent cardiac surgery twice for aortic and mitral valves immune-mediated degeneration. The neurologic event was secondary to Listeria monocytogenes aortic endocarditis, complicated by a cerebral embolism and periaortic abscess.

Discussion Patients with HUVS rarely present valvular heart disease. The latter is mostly secondary to an inflammatory process. Valve degeneration and immunosuppressive therapy increase the risk of infective endocarditis, with dramatic consequences for the prognosis of these patients. Valvular involvement is a sporadic but potentially fatal complication of HUVS, which should be taken in mind in the multidisciplinary evaluation of these patients.

Keywords Hypocomplementemic urticarial vasculitis syndrome • Valvular disease • Listeria monocytogenes endocarditis • Case report

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Learning points

- Severe valvular heart disease may complicate hypocomplementemic urticarial vasculitis syndrome, secondary to an inflammatory immune complex-mediated process. Prolonged immunosuppressive therapy increases the risk of infective endocarditis from rare agents, such as Listeria monocytogenes.
- Transthoracic echocardiography has a low sensitivity (50%) for infective endocarditis on prosthetic valves. In patients with possible infective endocarditis, transoesophageal echocardiography should be performed to exclude the diagnosis.
- After an intracranial haemorrhage, surgery should generally be postponed for at least 1 month, but this exposes the patient to the risk of endocarditis complications. Some authors recommend serial magnetic resonance imaging to assess the degree of intra-cerebral bleeding to help to guide the surgical timing.

Introduction

Hypocomplementemic urticarial vasculitis syndrome (HUVS) is a rare disease of small vessels characterized by chronic urticarial vasculitis, arthralgia, arthritis, and activation of the classical complement pathway. To the best of our knowledge, just other nine cases[1–7] of HUVS with cardiac valvular involvement have been reported in the literature. Unlike previous cases, ours shows an early and severe cardiovascular damage, absence of anti-C1q antibodies, and was not associated with deforming arthritis.

Timeline

Timeline	Description
10 years	Diagnosis of hypocomplementemic urticarial vasculitis syndrome
2 years	Multiple inflammatory valve damage treated with aortic valve repair, surgical mitral, and tricuspid annuloplasty
1 year	Relapse of valvular insufficiency treated with aortic and mitral valve replacement with bioprosthesis
2 months	Left pyelonephritis from Listeria monocytogenes treated with meropenem and gentamicin for 10 days
1 month	Remittent fever
Day 0	Admission to the emergency department after sudden onset of right hemiplegia, global aphasia, and reduced consciousness (Glasgow Coma Scale 9) • Brain computed tomography (CT): cerebral haemorrhage • Brain CT angiography: pseudoaneurysmatic mycotic dilatation • Transoesophageal echocardiogram: aortic valve endocarditis (abscess extending around the prosthesis and the aortic root) • Angiography: 7 mm large mycotic pseudoaneurysm in the M3 tract of left medium cerebral artery, treated with embolization • Empiric antibiotic therapy
Day 1	Neurosurgical haemorrhage evacuation
Day 2	Listeria monocytogenes isolation from blood culture. Treatment with ampicillin and gentamicin
Month 4	Coronary embolism and death

Case presentation

A 32-year-old woman was brought to the emergency department because of the sudden onset of right hemiplegia, global aphasia, and reduced consciousness (Glasgow Coma Scale 9). At admission, her vital signs were normal, artery pressure was 130/60 mmHg, heart rate 65 b.p.m., she had no hypoxia with normal peripheral oxygen saturation, and her body temperature was 36.8°C. The physical examination revealed a quiet holosystolic flow heart murmur grade 2 over the right second intercostal space, without radiation. Laboratory data showed microcytic anaemia due to a known thalassaemia trait; haemoglobin was 9.5 g/dL, mean corpuscular volume was 75.9 fL; white blood count, renal function, hepatic and cardiac enzymes, C reactive protein, and procalcitonin were normal.

She suffered from a severe HUVS form with cardiac valvular involvement. Hypocomplementemic urticarial vasculitis syndrome was diagnosed 10 years before, based on recurrent urticarial episodes with hypocomplementemia, associated with arthralgia, and a skin biopsy highlighting a leukocytoclastic vasculitis. After the diagnosis, the patient was treated with azathioprine and subsequently with mycophenolate, followed by steroids per os. Prolonged and high dosage steroid and immunosuppressive treatments exposed her to several systemic infections.

During these years, she had already undergone cardiac surgery twice for a chronic aseptic inflammatory process involving aortic and mitral valves. Indeed, she had been subjected 2 years before admission, at the age of 30 years, to cardiac surgery with aortic valve repair and mitral and tricuspid annuloplasty for severe aortic, mitral, and tricuspid regurgitation; 1 year before, at the age of 31 years, she underwent aortic and mitral valve replacement with biological prostheses for the relapse of aortic and mitral regurgitation. Regular cardiologic follow-up showed normal left ventricular and prosthetic function. Two months before admission, she reported left pyelonephritis from Listeria monocytogenes, treated with meropenem 3 g/day and gentamicin 2 mg/kg/day for 10 days. On this occasion, transthoracic echocardiography was unremarkable. During the month before

admission, she complained of remittent fever without other symptoms.

After admission, the patient underwent several instrumental examinations. A brain computed tomography (CT) without contrast medium showed a left frontoparietal haemorrhage 60 mm × 40 mm large, with perilesional oedema and midline shift of 13 mm (*Figure 1*). A CT angiography evidenced a lobulated vascular dilatation, which suggested a mycotic aneurysm, considering the history of remittent fever. A transthoracic echocardiogram revealed a paravalvular aortic thickening. A transoesophageal echocardiogram showed an echo lucent space with thickening at the aortic root consistent with an abscess extending around the aortic prosthesis, reaching the first part of the ascending aorta, with signs of internal colliquation, and a maximum thickness of 16 mm (*Figure 2* and *Video 1*). A CT angiography of the aorta confirmed the diagnosis, showing a collection of fluid density around the aortic root (*Figure 3*).

Right hemiplegia and global aphasia were caused by septic embolism to the left medium cerebral artery complicated by cerebral haemorrhage. Angiography confirmed a 7 mm sizable mycotic pseudoaneurysm in the M3 tract of the left medium cerebral artery (*Figure 4*). After a multidisciplinary consult, endovascular treatment was chosen. A super-selective catheterization of the aneurysm allowed the injection of Glubran inside it, a cyanoacrylate-based synthetic glue, obtaining a complete angiographic obliteration. The day after, the patient underwent neurosurgical evacuation of the haemorrhage. Listeria monocytogenes was isolated from blood

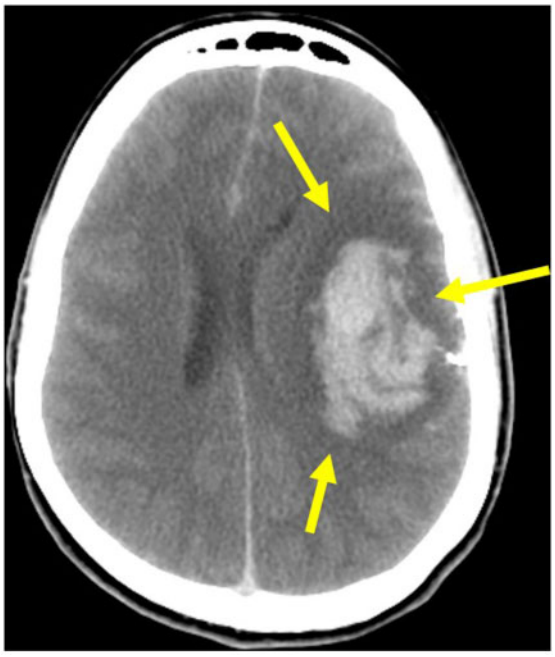
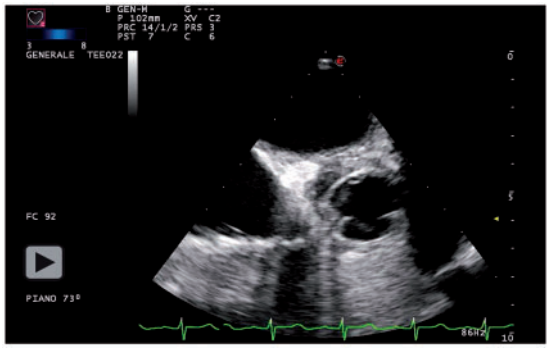


Figure 1 Brain computed tomography without contrast medium showing a left frontoparietal haemorrhage 60 mm × 40 mm large, with perilesional oedema, and midline shift of 13 mm.



Video 1 Transoesophageal echocardiography showing the periaortic abscess, short axis.

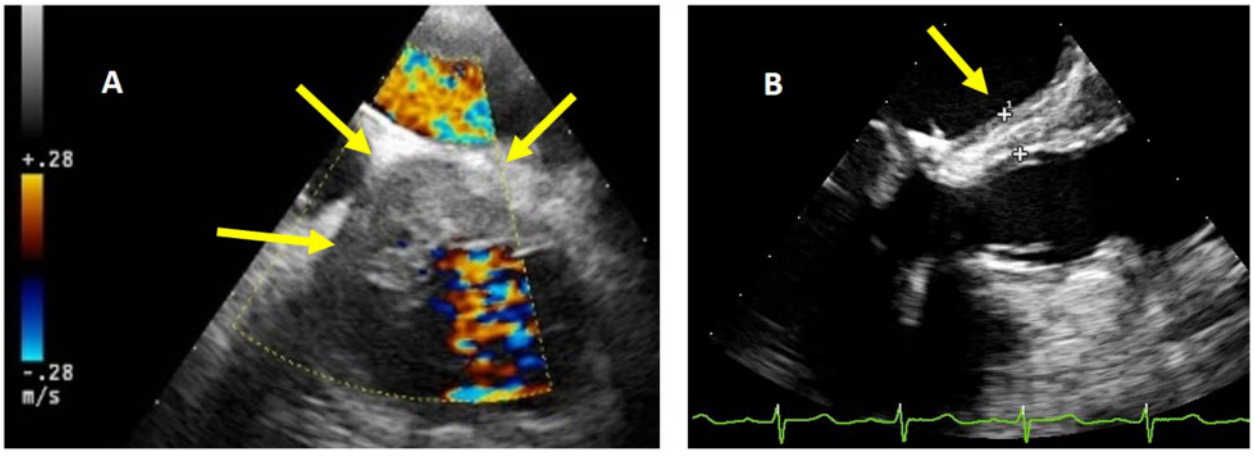


Figure 2 Transoesophageal echocardiography showing an echo lucent space with thickening at the aortic root consistent with an abscess extending around the aortic prosthesis (*A*, short axis), reaching the first part of the ascending aorta (*B*, 129°).

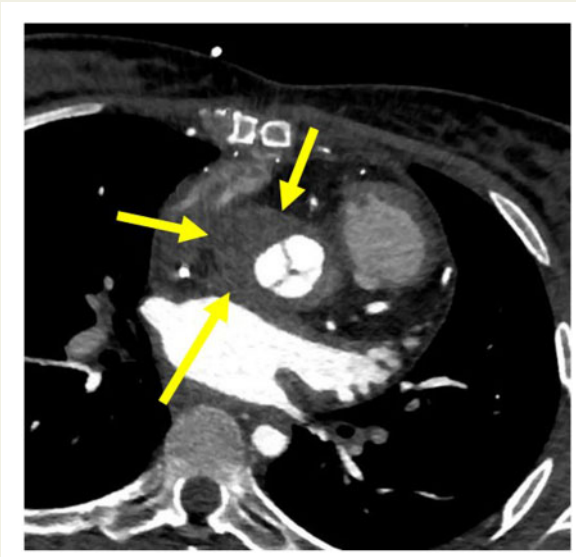


Figure 3 Computed tomography angiography showing a collection around the aortic root consistent with a periaortic abscess.

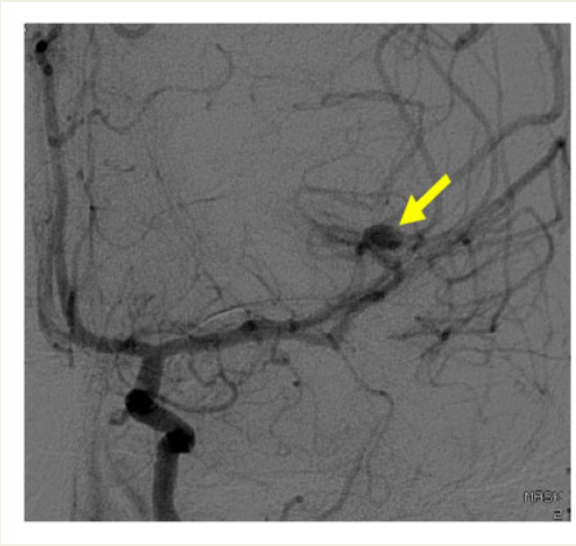


Figure 4 Cerebral selective left carotid angiography showing a lobulated, saccular, 7 mm aneurysm in the M3 tract of the left medium cerebral artery.

cultures; it was the agent responsible for aortic infective endocarditis, probably secondary to prolonged immunosuppressive therapy.

The patient responded to antibiotic treatment with ampicillin 12 g/day, levofloxacin 1000 mg/day, and linezolid 1200 mg/day, and a subsequent transoesophageal ultrasound exam showed a reduction of the abscess engagement after 54 days of therapy. At admission, she was taking deltacortene 12.5 mg/day as a maintenance dose. We continued this therapy after the diagnosis of endocarditis to prevent a vasculitis flare-up. During antibiotic therapy, she was afebrile. A progressive neurological improvement occurred during hospitalization. The patient was directed towards a rehabilitation plan, with the purpose to evaluate elective aortic prosthesis replacement after the improvement of general conditions.

Further cardiac surgery would have been necessary, but the operative risk was judged too high. The patient died a few months later for an endocarditis relapse, causing a coronary embolism.

Its clinical complexity makes this case a rarity in rarity, in a disease context that is not yet fully understood.

Discussion

A diagnosis of HUV requires two major criteria and at least two minor criteria. The major criteria are recurrent urticaria for over 6 months and hypocomplementemia. The minor criteria include leukocytoclastic vasculitis on biopsy, joint pain or arthritis, glomerulonephritis, ocular inflammation (uveitis, episcleritis), recurrent abdominal pain, or anti-C1q antibodies.[1]

The association between HUVS and cardiac valvular disease has rarely been described in the literature, and most cases, in combination with Jaccoud's arthropathy.[1–7] The presence of valvular involvement is an adverse prognostic factor.

The anatomopathological evaluation of her native valves showed the typical valve involvement of this disease, with fibrinoid deposits and granulocyte infiltrates.

Other reports have described acute necrotizing endocarditis and fibrin deposition on the surface of valve leaflets, with signs of chronic inflammation, comprising lymphocytes and histiocytes, fibrocalcific degenerative changes, and positive staining for IgG, IgA, IgM, and light-chain determinant-bearing proteins at the valve surface.[4]

Unlike most cases with valvular involvement, our patient was negative for anti-C1q antibodies, did not have Jaccoud's hands deformity, and exhibited a highly severe cardiac disease, needing two surgical interventions. Most previous cases[1–7] were treated with high-dose steroid therapy and immunosuppressive therapy with either azathioprine, cyclophosphamide, or mycophenolate mofetil, but no other case was complicated by infective endocarditis.

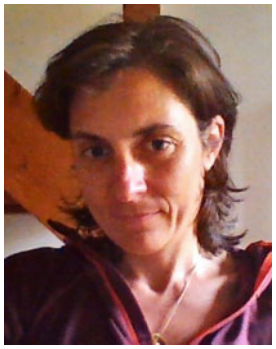
Listeria monocytogenes endocarditis ultimately aggravated the patient's condition. This complication is also a rare condition associated with a high mortality rate. Listeria monocytogenes is an aerobic, gram-positive coccobacillus. It is a transient colonizer of the human gastrointestinal tract; infection does not occur unless host factors promoting invasive disease are present, such as immunosuppression. The primary infection from Listeria monocytogenes was pyelonephritis, with subsequent localization on the aortic valve. Endocarditis is observed in ~8% of adults infected with Listeria monocytogenes and occurs on native and prosthetic valves. The echocardiography performed at the time of the urinary infection was unremarkable. Still, transthoracic echocardiography has a low sensitivity (50%) for infective endocarditis on prosthetic valves,[8] and this might have delayed the diagnosis. Penicillin and ampicillin (as monotherapy) are the drugs most frequently used to treat this microbiological agent.[9,10] Given the paravalvular extension of the infection, a further surgical intervention would have been the therapy of choice, but the patient's clinical conditions did not allow this strategy. While cardiac surgery is not

contraindicated after an ischaemic embolic stroke complicating infective endocarditis, in cases with intracranial haemorrhage, surgery should generally be postponed for at least 1 month.[8] Some authors[11] recommend serial magnetic resonance imaging to assess the reduction in the degree of intra-cerebral bleeding to help to guide the surgical timing.

Conclusions

The multidisciplinary evaluation of patients with HUVS should consider valvular heart disease. The latter is probably an immune complex- and cellular-mediated inflammation. Valve degeneration and immunosuppressive therapy increase the risk of infective endocarditis, with dramatic consequences for the prognosis of these patients.

Lead author biography



Valentina Scheggi graduated in Medicine from Florence University in July 2001 and specialized in Internal Medicine in October 2006. She got the certification from SIECVI in echocardiography in 2006 and in echo stress in 2010. She worked as emergency physician at the emergency department of the Florence University Hospital from 2008 to 2012, when she began to work in the cardiologic and peri-operative Internal Medicine department of the same hospital, where she still works. During the last 5 years this department increased the collaboration with the cardiosurgical one, allowing her to gain a great experience in the clinical management and echocardiographic evaluation of surgical patients.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The patient reported in this case is deceased. Despite the best efforts of the authors, they have been unable to contact the patient's next-of-kin to obtain consent for publication. Every effort has been made to anonymize the case. This situation has been discussed with the editors.

Conflict of interest: None to declared.

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References

1. Amano H, Furuhata N, Tamura N, Tokano Y, Takasaki Y. Hypocomplementemic urticarial vasculitis with Jaccoud's arthropathy and valvular heart disease: case report and review of the literature. *Lupus* 2008;**17**:837–841.
2. Park C, Choi SW, Kim M, Park J, Lee JS, Chung HC. Membranoproliferative glomerulonephritis presenting as arthropathy and cardiac valvulopathy in hypocomplementemic urticarial vasculitis: a case report. *J Med Case Rep* 2014;**8**:352.
3. Chen HJ, Bloch KJ. Hypocomplementemic urticarial vasculitis, Jaccoud's arthropathy, valvular heart disease, and reversible tracheal stenosis: a surfeit of syndromes. *J Rheumatol* 2001;**28**:383–386.
4. Houser SL, Askenase PW, Palazzo E, Bloch KJ. Valvular heart disease in patients with hypocomplementemic urticarial vasculitis syndrome associated with Jaccoud's arthropathy. *Cardiovasc Pathol* 2002;**11**:210–216.
5. Hauser B, McRorie E, McKay N, Brenn T, Amft N. A case of hypocomplementaemic urticarial vasculitis with cardiac valve involvement successfully treated with cyclophosphamide and high-dose glucocorticoids. *Int J Rheum Dis* 2017;**20**:1850–1852.
6. Palazzo E, Bourgeois P, Meyer O, De Bandt M, Kazatchkine M, Kahn MF. Hypocomplementemic urticarial vasculitis syndrome, Jaccoud's syndrome, valvulopathy: a new syndromic combination. *J Rheumatol* 1993;**20**:1236–1240.
7. Hong L, Wackers F, Dewar M, Kashgarian M, Askenase PW. Atypical fatal hypocomplementemic urticarial vasculitis with involvement of native and homograft aortic valves in an African American man. *J Allergy Clin Immunol* 2000;**106**:1196–1198.
8. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F et al.; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015;**36**:3075–3128.
9. Summa C, Walker SAN. Endocarditis due to listeria monocytogenes in an academic teaching hospital: case report. *Can J Hosp Pharm* 2010;**63**:312–314.
10. Valckx W, Lutgens SPM, Haerkens-Arends HE, Barneveld PC, Beutler JJ, Hoogeveen EK. Listeria endocarditis: a diagnostic challenge. *J Investig Med High Impact Case Rep* 2017;**5**:2324709617698995.
11. Bhattacharyya S, Oo A. Timing of surgery after secondary embolic events in infective endocarditis. *Ann Cardiothorac Surg* 2019;**8**:688–690.