IgA Vasculitis With Henoch-Schönlein Purpura as an Immune Complication Associated With Left Ventricle Assist Device Insertion

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The implantation of left ventricular assist devices (LVADs) in patients with end-stage heart failure can be associated with some forms of immune dysregulation and systemic inflammatory response. These abnormalities may be related to impaired T-lymphocyte-dependent immunity and B-lymphocyte hyperreactivity and may lead to the development of autoimmune processes and the occurrence of severe infections. We present here the first observation of a peculiar immune complication associated with the implantation of an LVAD, characterized by an IgA vasculitis clinically manifested as Henoch-Schönlein purpura. The vasculitis was biologically associated with a significant increase of the plasma levels of C-X-C motif chemokine ligand (CXCL)13, a CXC motif chemokine produced by follicular dendritic cells, which targets CXCR5, a receptor primarily expressed by B lymphocytes, to promote their chemotaxis and expansion. Spontaneous resolution of the vasculitis occurred over time, concomitantly to a decrease of CXCL13 expression. These findings suggest that CXCL13 might be an interesting biomarker to detect auto-antigen sampling and the risk of secondary immune complications following LVAD implantation. *ASAIO Journal* 2022; 68;e67–e70

Key Words: Henoch-Schönlein purpura, IgA vasculitis, mechanical circulatory support, LVAD, autoimmune disease

Although the implantation of durable left ventricular assist devices (LVADs) has become a key therapeutic option in end-stage heart failure, the presence of foreign material within such devices may be associated with various immune disturbances.[1] We report for the first time a peculiar immune complication associated with the implantation of a Heartmate 3 (Abbott) centrifugal flow LVAD, under the form of a spontaneously resolutive systemic IgA vasculitis, known as Henoch-Schönlein purpura,[2] which was associated with very high plasma levels of the B lymphocyte chemoattractant cytokine C-X-C motif chemokine ligand (CXCL)13.[3]

Case Report

A 70-year-old man with stage III chronic heart failure was referred to our center for LVAD implantation. Except for atrial fibrillation, high blood pressure, and chronic obstructive pulmonary disease, medical history was unremarkable, notably without any previous inflammatory or immune disorder. During the operation for the implantation of a HeartMate 3 LVAD, we noticed a heavily calcified ascending aorta, which required us to perform the outflow graft anastomosis under aortic cross-clamp with cardioplegic arrest. After weaning from cardiopulmonary bypass, the patient presented severe right heart failure, requiring temporary right ventricular support, using an extracorporeal circuit between a femoral venous inflow cannula and an outflow cannula into the main pulmonary artery trunk. In the first postoperative hour, the patient developed acute lung injury with massive pulmonary fluid leakage, requiring large amounts of intravenous fluids. To interrupt the pulmonary fluid losses, we wanted to reduce as much as possible transpulmonary blood flow and decided to bypass the pulmonary circulation by converting the veno-pulmonary circuit into a veno-aortic extracorporeal membrane oxygenation (ECMO) support. As this setup would compromise adequate LVAD preload and lead to a drastic reduction of the LVAD flow with a high risk of pump thrombosis, the HeartMate 3 flow was interrupted and the aortic outflow cannula oversewn to avoid backflow into the left ventricle. This central approach was used because both femoral arteries were calcified and not suitable for peripheral cannulation. Furthermore, to avoid additional manipulation of the calcified ascending aorta, we chose to insert the ECMO outflow cannula through the HeartMate 3 outflow cannula, thus sacrificing the HeartMate 3 pump.

After resolution of the acute lung injury, ECMO was weaned on postoperative day (POD) 10, and the HeartMate 3 pump was exchanged for a new device. During reoperation, we did no notice any novel peculiarities of the aorta (calcified) and the pulmonary trunk. The postoperative course was complicated by transient acute renal failure requiring dialysis and ventilator-associated pneumonia due to Gram-negative bacteria treated with piperacillin–tazobactam. On POD 55, the patient developed diffuse purpura on hands, legs, and buttocks (Figure 1A and B), with no associated thrombocytopenia and with a plasma C-reactive protein (CRP) value of 98 mg/L. A skin biopsy revealed a leukocytoclastic vasculitis of small superficial vessels, and direct immunofluorescence disclosed IgA and complement C3

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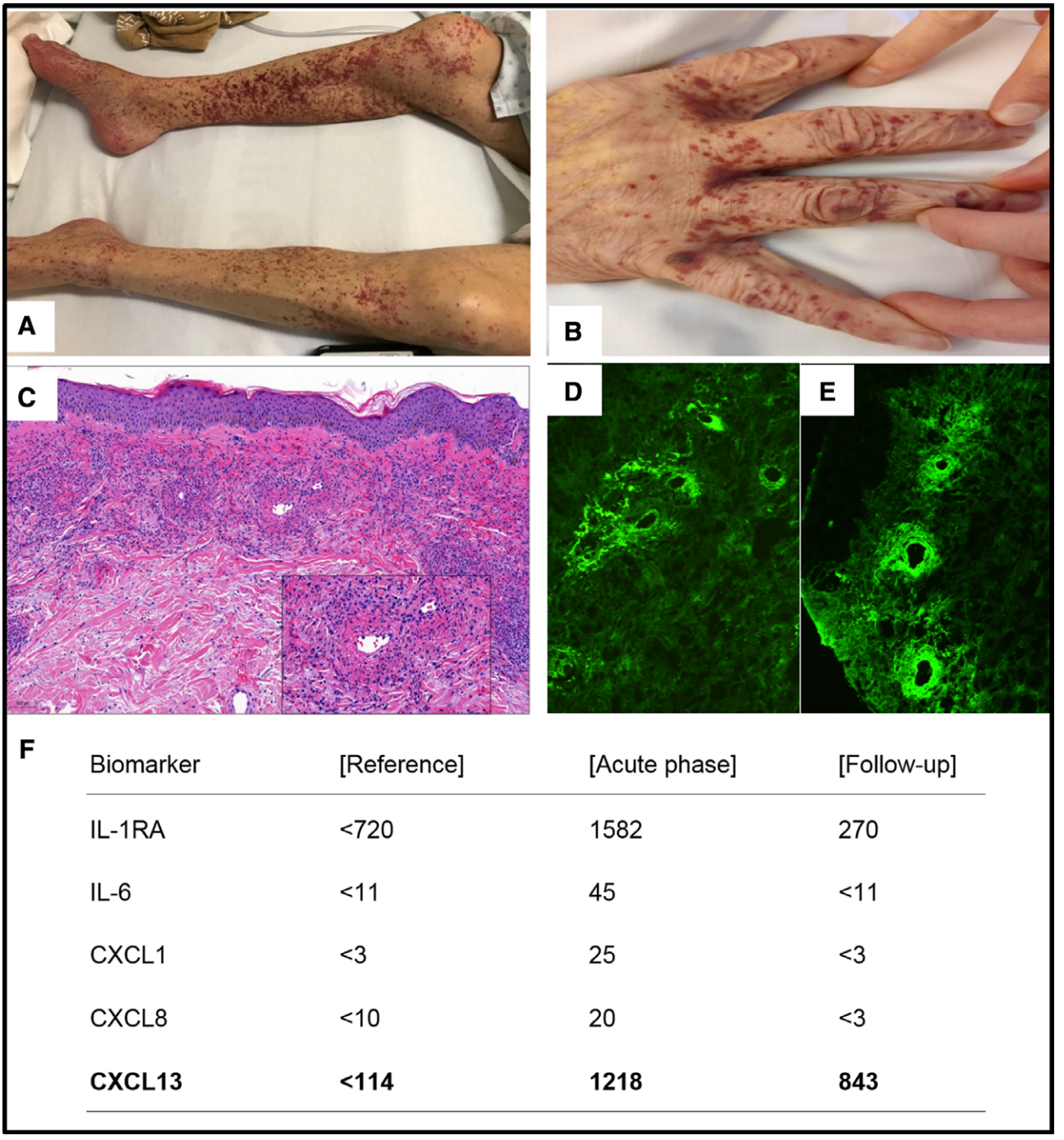

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Biomarker	[Reference]	[Acute phase]	[Follow-up]
IL-1RA	<720	1582	270
IL-6	<11	45	<11
CXCL1	<3	25	<3
CXCL8	<10	20	<3
CXCL13	**<114**	**1218**	**843**

Figure 1. IgA vasculitis manifested as Henoch-Schönlein purpura following LVAD implantation. **A** and **B**: Clinical aspect of the palpable purpura on legs and hands. **C**: Leukocytoclastic vasculitis demonstrated on histopathologic examination of dermal vessels, characterized by dense perivascular neutrophil infiltrates with red blood cell extravasation. The vascular walls of the superficial plexus (insert) show marked thickening with fibrin deposition and inflammatory cell infiltration (Hematoxylin-eosin staining, magnification x100). **D** and **E**: Immunoglobulin A and complement C3 deposits within the walls of dermal vessels, demonstrated by direct immunofluorescence (x10 magnification). **F**: Cytokines and chemokines at the acute phase and after recovery of the vasculitis. A persistently marked elevation for CXCL13 (bold) was the main abnormality. CXCL, C-X-C motif chemokine ligand.

deposits in vessel walls (Figure 1C–E). Urinalysis showed microscopic hematuria (113×10^6 red blood cells/mL) and mild proteinuria (1g/L), pointing to glomerular involvement. A diagnosis of Henoch-Schönlein purpura (IgA vasculitis) was made. In the absence of significant renal involvement, the patient was treated with topical corticosteroids, leading to complete resolution of the purpura on POD 79. To explore potential immune abnormalities associated with vasculitis, we measured a panel of cytokines, chemokines, and growth factors (Table 1). At the acute phase, we noted a slight increase of Interleukin-6, Interleukin-1 receptor antagonist (IL-1-Ra), and of the chemokines CXCL1 and CXCL8, but the most noticeable abnormality was a striking

Table 1. Cytokines, Chemokines and Growth Factors at the Acute Phase and After Recovery of Henoch-Schönlein Purpura (all values in pg/mL)

Biomarker	Reference	Acute phase	Follow-up
IL-1α	<6	<1	<1
IL-1RA	<720	**1582**	270
IL-1β	<4	4	<3
IL-2	<13	13	<6
IL-4	<13	<13	<13
IL-5	<13	<13	<13
IL-6	<11	45	<11
IL-7	<3	1	<1
IL-9	<9	<9	<9
IL-10	<3	<3	<3
IL-12p70	<13	<13	<13
IL-13	<6	<6	<6
IL-15	<13	13	<4
IL-17a	<4	<3	<3
IL-18	<22	<18	<18
IL-21	<43	<13	<13
IL-22	<55	<26	<26
IL-23	<19	<19	<19
IL-27	<28	<26	<26
IL-31	<15	<15	<15
IFNα	<1	<1	<1
IFNγ	<16	<16	<16
TNFα	<12	<12	<12
CCL2	<113	35	10
CCL3	<42	7	<2
CCL4	<247	65	18
CCL11	<199	86	40
CXCL1	<3	**25**	<3
CXCL8	<10	**20**	<3
CXCL9	<16	<23	9
CXCL12	<701	660	187
CXCL13	<114	**1218**	**843**
NGFβ	<43	<8	<8
BDNF	<261	187	5
EGF	<118	16	<3
FGF-2	<32	<4	<4
LIF	<23	10	<6
PDGF-BB	<171	27	<8
PIGF-1	<328	6	<2
VEGF-A	<569	184	369
BAFF	<8	<8	<8
GM-CSF	<18	<18	<8

Abnormal values are indicated in bold.

BAFF, B-cell activating factor belonging to the tumor necrosis factor family; BDNF, brain derived neurotrophic factor; CCL, C-C motif chemokine ligand; CXCL, C-X-C motif chemokine ligand; EGF, epidermal growth factor; FGF, fibroblast growth factor; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LIF, leukemia inhibitory factor; NGF, nerve growth factor; PDGF-BB, platelet-derived growth factor, two B subunits; PIGF, placenta growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

elevation of the B lymphocyte attracting chemokine CXCL13 (Figure 1F), at 11 times the reference value. Following recovery from the purpura (on a follow-up visit at POD 179), plasma CXCL13 was lowered but still remained elevated at approximately seven times the reference value. No long-term sequelae were noted in the patient who remained in good clinical condition at 12 months follow-up, without any recurrence of the skin lesions.

Discussion

This case is the first report of a spontaneously resolutive Henoch-Schönlein purpura (HSP) complicating LVAD implantation, as shown by nonthrombocytopenic palpable purpura, mild glomerular involvement, and prototypical histopathologic changes of a small vessel vasculitis with IgA and C3 deposition in the wall of dermal vessels.[2] The nature of the antigen to which IgA binds in HSP is presently unknown but is believed to be from endothelial origin.[2] HSP is the most common systemic vasculitis in children, but it is infrequent in adults, where it has been associated with tumors, viral and bacterial infections (staphylococci and streptococci), and drugs including quinolones and clarithromycin.[4] None of the aforementioned causes of HSP were present in our patient, supporting that the vasculitis developed as a peculiar immune complication associated with the implanted LVAD.

It must be underscored that the patient was initially exposed to multiple extracorporeal circuits, including two cardiopulmonary bypass circuits, one femoro-pulmonary right ventricular support, and one VA-ECMO circuit, in addition to the two implanted HeartMate 3 LVADs. The patient also exhibited significant pulmonary inflammation after the initial surgery. Obviously, the foreign material associated with the multiple devices, as well as the early lung inflammatory response, may all have contributed to promote some form of immune disturbances, and the unique and specific contribution of the HeartMate3 LVAD can therefore not be formally ascertained. A plausible pathophysiologic scenario could be that several additional immunologic insults concurred to the delayed development of HSP in this patient.

Previous studies indicated that LVAD may be indeed associated with some forms of immune dysregulation and systemic inflammatory response, which holds true for any form of VADs, but not specifically to the HeartMate 3 device.[1] Recipients of first-generation pulsatile LVADs displayed impaired T-lymphocyte-dependent immunity, together with evidence of B-lymphocyte activation.[5] The pseudo-neointima cellular lining that covers blood-contacting LVAD surfaces could play a role in triggering these immune complications, notably by hosting monocytes and activated macrophages.[5] These immune cells may trigger CD95-dependent T-cell apoptosis, leading to a selective loss of $CD4^+$T cells producing Th1 cytokines, with unopposed production of Th2 cytokines.[5] In turn, Th1/Th2 imbalance combined with B cell hyper-reactivity may promote autoimmune processes and the occurrence of severe infections.[1,5]

At the time of HSP development, three salient features could be determined. The first one was a persistent increase of CRP together with moderate elevations of IL-6 and IL-1Ra, as well as a slight increase in neutrophil attractant chemokines (CXCL1 and CXCL8, or IL-8), consistent with a nonspecific systemic inflammation, as frequently observed following LVAD implantation.[1] The second one was the absence of any changes in both Th1 (IL-2 and interferon γ) and Th2 cytokines (IL-4, IL-5, IL-10, and IL-13), indicating no evidence of a skewed Th1/Th2 balance. The third and most significant finding was a markedly elevated level of CXCL13 at the time of HSP occurrence, with a partial decrease following HSP resolution. Such elevation of CXCL13 and the fact that its levels paralleled the clinical course support a pathophysiologic link between CXCL13 and HSP in this situation.

CXCL13, formerly B cell-Attracting Chemokine 1 (BCA-1), is a CXC motif chemokine whose specific receptor is CXCR5, formerly BLR1 (Burkitt's Lymphoma Receptor 1), a G

protein-coupled receptor primarily expressed by B lymphocytes, but also by follicular helper T-cells (T_{FH}).[3] CXCL13 is produced in lymphoid follicles by follicular dendritic cells to promote chemotaxis, expansion, and differentiation of B lymphocytes. A dysregulation of the CXCL13:CXCR5 axis, affecting both B lymphocytes and T_{FH} cell functions, has been implicated in the pathogenesis of autoimmune diseases (myasthenia gravis, rheumatoid arthritis, and systemic lupus erythematosus), infectious diseases (HIV 2 infection, Lyme neuroborreliosis, and neurosyphilis) and solid tumors,[3] but there has been no description so far of its role in the development of HSP. In the case under discussion, we may hypothesize that the repeated exposure to foreign intravascular material, endothelial damage, and the formation of pseudo-neointimal tissue in the LVAD cannulas promoted the release of some putative endothelial autoantigens. Subsequent sampling of these antigens in lymphoid tissue by follicular dendritic cells may have triggered a CXCL13:CCR5 dependent activation of autoreactive, IgA-producing B lymphocytes, and the development of IgA vasculitis. Interestingly, the plasma level of CXCL13 decreased but still remained elevated upon clinical recovery of HSP, which could denote the persistence of the auto-antigenic stimulus, albeit at a level insufficient to sustain the vasculitis process.

Conclusions

This case illustrates a previously unreported immune complication associated with the implantation of an LVAD, characterized by an IgA vasculitis coincident with the expression of the B lymphocyte chemoattractant cytokine CXCL13. These findings suggest that CXCL13 might be an interesting biomarker to detect auto-antigen sampling and the risk of secondary immune complications following LVAD implantation.

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