Antiphospholipid antibodies, cryoglobulinemia and IgM kappa monoclonal gammopathy in recurrent small vessel thrombosis: a case report

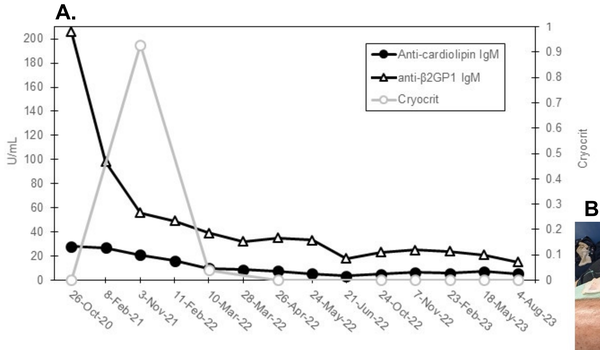
Alexandra Bohm[1], Bo Angela Wan[1], Amir Karin[2], Lauren J Lee[3], Agnes YY Lee[3], Edward M Conway[4] and Chieh Min Benjamin Lai[3]

1 Department of Medicine, University of British Columbia, Vancouver BC, Canada, 2 Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada,
3 Division of Hematology, Department of Medicine, University of British Columbia, Vancouver, BC, Canada, 4 University of British Columbia Centre for Blood Research, Vancouver, BC, Canada
emal: akbohm@student.ubc.ca

Introduction

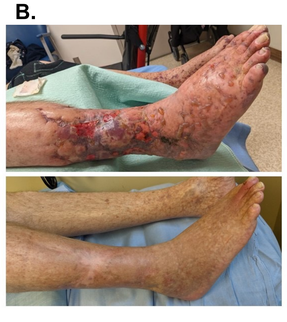
Antiphospholipid syndrome (APS) is a thrombo-inflammatory disease associated with recurrent thrombosis in macro as well as microvasculature[1,2]. It is driven by autoantibodies that induce activation of immune cells, complement, endothelium, and the coagulation cascade[3]. Cryoglobulinemia is similarly an autoimmune disorder characterized by autoreactive antibodies, inflammatory cell recruitment, occlusive vasculopathy, complement activation, and small vessel thrombosis. Specifically, type 1 cryoglobulinemia is associated with monoclonal gammopathies, some of which are of uncertain significance (MGUS) and others that are associated with B-cell malignancy[4,5]. The term "monoclonal gammopathy of thrombotic significance" has been proposed to capture diseases where a thrombogenic paraprotein causes significant or recurrent thrombosis[6]. The shared relationship of prothrombotic autoreactive antibody suggests possible overlap between different disease entities. Individuals with overlap conditions may therefore represent a unique high risk patient population who require closer monitoring and B-cell directed treatment. However, data to support the interplay of these conditions remain scarce.

Case evolution



A. Improvement in anti-phospholipid titers (anti-cardiolipin IgM, anti-β2GP1) and cryoglobulin over time.

B. Photos of the necrotic ulcers before and after treatment



Overlap of APS, MGUS and cryoglobulin

ID	APS test results	APS ELISA	Cryoglobulin	Monoclonal protein	Clinical diagnosis
1	LA positive (on heparin) aβ2GP1 IgG 358 aβ2GP1 IgM <0.8 aCL IgG 48 aCL IgM 5.5	ELiA	Negative	5.5 g/L IgG lamda	Recurrent stroke, finger ischemic ulcer, monoclonal B-lymphocytosis
2	LA positive (on warfarin) aβ2GP1 IgG 98 aβ2GP1 IgM <0.8 aCL IgG 80 aCL IgM 1.2	ELiA	Not done	Faint IgG kappa	Recurrent stroke, myocardial infarction, TIA, stroke, ITP, marginal zone lymphoma
3	LA positive aβ2GP1 IgG >160 aβ2GP1 IgM 0.3 aCL IgG >160 aCL IgM 0.3	BioPlex	Not done	0.4 g/L IgG kappa	PE, recurrent DVT
4	LA negative aβ2GP1 IgG <1.6 aβ2GP1 IgM 3.3 aCL IgG 2.4 aCL IgM 27.0	BioPlex	Negative	Faint IgA lambda	PE, recurrent DVT
5	LA positive aβ2GP1 IgG 6.3 aβ2GP1 IgM <0.8 aCL IgG 4.6 aCL IgM 2.3	BioPlex	Negative	2.1 g/L IgG kappa	Stroke, seizure

- Reviewed 118 patients with at least one positive APS antibody test
- 69 patients had cryoglobulin testing done but none had significant cryocrit
- 91 patients had SPEPs done and 7 patients (7.7%) had a monoclonal gammopathy
- 3/7 patients had a paraprotein of the same isotype as the APS antibody

Case report

August 2020

- 61-year-old man presented with painful bilateral necrotic ulcers on the shins.
- Skin biopsy: superficial dermal vascular thrombosis with minimal inflammation and prominent fibrin thrombi in the capillary lumen with no evidence of small vessel leukocytoclastic vasculitis
- Strongly positive for:
  - Anti-beta-2-glycoprotein-1 (anti-β2GP1) IgM
  - Weakly positive for anticardiolipin (aCL) IgM
  - Negative for lupus anticoagulant
  - Serum protein electrophoresis (SPEP) showed 0.7 g/L monoclonal IgMκ
  - Cryocrit was negative
- Improved with aspirin 81 mg daily plus warfarin with standard target INR 2.0-3.0.

October 2021

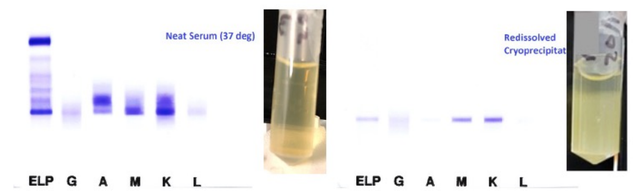
- Returned with purpuric, and gangrenous lesions on his right foot and shin.
- He had an excisional left inguinal lymph node biopsy which was consistent with marginal zone lymphoma.
- Serum now showed:
  - Positive cryoglobulins with a cryocrit of 95%
  - Persistently positive antiphospholipid antibodies
  - SPEP demonstrated a 10 g/L IgMκ paraprotein and a smaller IgAκ band
- Improved with aspirin 81 mg daily plus warfarin with high target INR 2.5-3.5

February 2022

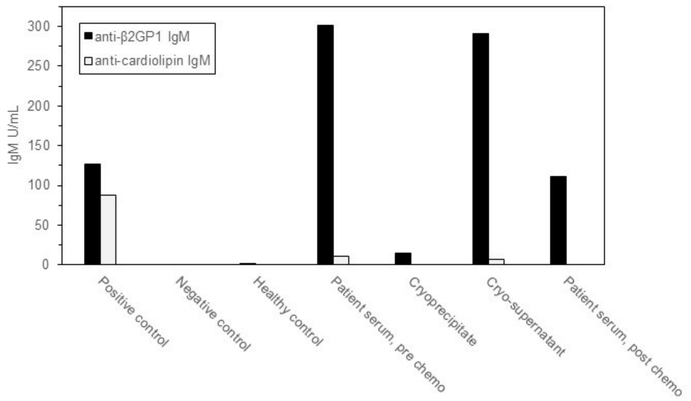
- Recurrence of painful, necrotic ulcers in his right leg
- Started chemoimmunotherapy with bendamustine and rituximab for lymphoma
- Ulcers completed resolved by 3rd cycle of chemotherapy
- Serum now showed:
  - Undetectable cryoglobulin
  - APS antibodies downtrending
  - Cryoglobulin and IgMκ paraprotein were undetectable

Differentiating the auto-antibodies

Are the patient's new cryoglobulin antibodies that appeared in October 2021 IgMκ?



Are the patient's new IgMκ cryoglobulin antibodies that appeared in October 2021 also the APS antibodies?



Conclusions

- The patient's cryoglobulin antibodies were the known IgMκ paraprotein
- Most the patient's APS antibodies were detected in the supernatant but some remain detectable in the cryoglobulin fraction
- Pathological APS antibodies may be polyclonal and distinct from the cryoglobulin antibody and IgMκ paraprotein
- Alternatively, small amount of APS antibody detected in the precipitated fraction may be the pathological one; the APS antibody may be the same entity as the cryoglobulin and IgMκ paraprotein
- APS patients who potentially have monoclonal gammopathy of thrombotic significance require closer clinical surveillance and consideration of alternative treatments such as B cell targeting

References and acknowledgements

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