A case of IgA-antiphospholipid syndrome – a rare clinical variant

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Keywords

Antiphospholipid syndrome, beta-2-glycoprotein IgA, vasculopathy, ulcus cruris

Summary

IgA subtype antiphospholipid syndrome is a variant within the antiphospholipid syndrome group. It is also associated with a significantly increased risk of thrombembolic complications, as is the IgG antiphospholipid syndrome, IgM isotype. The clinical picture on the skin is varied, ranging from livedo racemosa to ulcers cruris and disseminated vasculitic lesions. Especially the vasculitic changes can best be explained by the properties of the immunoglobulin subtype. The addition of IgA antibodies and a skin biopsy is often helpful for further diagnosis and differentiation of other differential diagnoses.

Schlüsselwörter

Antiphospholipid-Syndrom, beta-2-Glycoprotein-IgA, Vaskulopathie, Ulcus cruris

Zusammenfassung

Das Antiphospholipid-Syndrom vom IgA-Subtyp ist eine Variante innerhalb der Erkrankungsgruppe des Antiphospholipid-Syndroms. Es ist ebenso mit einem deutlich erhöhten Risiko für thrombembolische Komplikationen assoziiert wie das Antiphospholipid-Syndrom vom IgG, IgM-Isotyp. Das klinische Bild an der Haut ist mannigfaltig, es reicht von einer Livedo racemosa, über Ulcera cruris bis hin zu disseminiert auftretenden, vaskulitisch imponierenden Läsionen. Vor allem die vaskulitischen Veränderungen lassen sich am ehesten durch die Eigenschaften des Immunglobulin-Subtyps erklären. Zur weiteren Diagnosesicherung und Abgrenzung anderer Differentialdiagnosen ist die Hinzunahme von IgA-Antikörpern sowie eine Hautbiopsie oft hilfreich.

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Background

Antiphospholipid syndrome (APS), first described in 1959 by P. Hughes and P.G.I. Stovin (1), is a systemic autoimmune disease characterised by the increased occurrence of thromboembolic events (2). According to recent studies, the frequency of APS in the general population is 1–5% with a marked female predilection (3).

APS manifests itself through recurrent arterial and venous thrombosis and, in women of child-bearing age, complications of pregnancy such as early abortion and miscarriages. The disease often has an episodic course and disease-free intervals can last for weeks, months or even years (4,5).
Criteria for the classification of the disease were drawn up for the first time in 1999 by an expert committee in Sapporo, Japan (6). According to the consensus paper of 2006 (7) the following criteria are now to be used to classify the disease:

Clinical criteria:

a) Vascular thrombosis – one or more episodes of arterial, venous or small-vessel thrombosis
b) Pregnancy morbidity
   - One or more stillbirths of a morphologically normal foetus
   - One or more premature births
   - Three or more consecutive spontaneous abortions

Laboratory criteria:

a) Anticardiolipin antibody of the IgG and/or IgM isotype in serum or plasma, present in medium or high titre at two or more examinations at least 12 weeks apart, measured by standardised techniques
b) Beta-2 glycoprotein-I antibody of the IgG and/or IgM isotype in serum or plasma, present in medium or high titre at two or more examinations, at least 12 weeks apart, measured by standardised techniques
c) Lupus anticoagulant present in plasma at two or more examinations at least 12 weeks apart (according to the International Society on Thrombosis and Haemostasis guidelines)

Case

Disease history

A young, 35-year old female patient presented at our outpatient clinic in 2016 with a 10-year history of recurrent small ulcers in the ankle and knee area. A diagnostic workup was undertaken. The vasculitis workup, including current antiphospholipid antibodies such as antibodies to cardiolipin, beta-2 glycoprotein I and lupus anticoagulant, had been normal several times in the past, so that despite the lack of duplex ultrasound and clinical correlation, compression therapy had been recommended

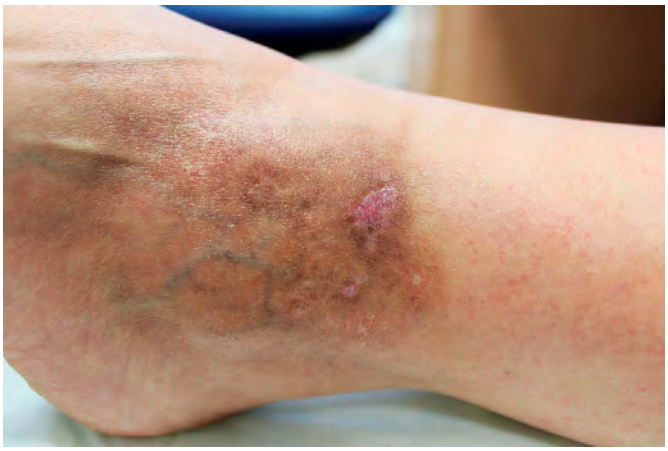

Fig. 1
Healing ulcers above the left lateral malleolus together with hyperpigmentation and atrophie blanche-like areas

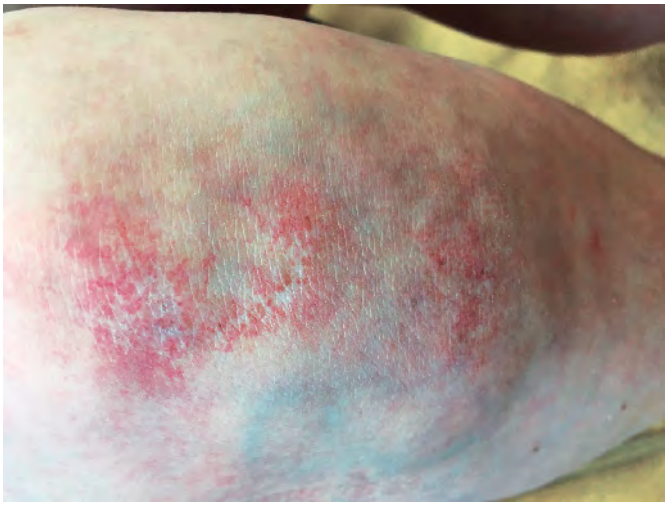

Fig. 2
Groups of teleangiectatic changes disseminated across both legs

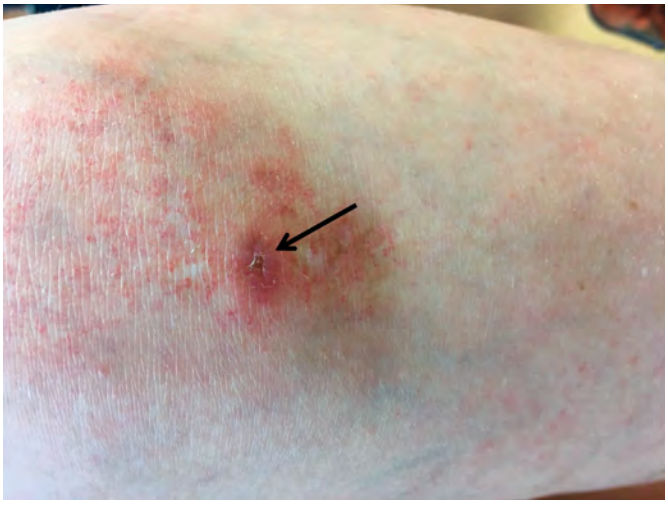

Fig. 3
Groups of teleangiectatic changes disseminated across both legs together with porcelain-coloured small scars and a florid ulcer (arrow)

externally, based on a diagnosis of chronic venous insufficiency.

Thorough history-taking revealed neither miscarriages nor stillbirths and no arterial or venous thrombotic events in the large vessels. The patient described a worsening of the findings predominantly in the summer months.

Clinical manifestation

On presentation, we saw ulcers of 0.5 cm in diameter with a punched-out appearance on the lateral aspect of both knees and bilaterally in the region of the medial and lateral malleolus, with hyperpigmentation of the surrounding dermis. In addition to these changes, there were areas of ectatic small blood vessels on both legs (▶ Figs. 1–3). Typical signs of chronic venous insufficiency such as calf oedema, paraplantar corona phlebectatica or trophic changes to the calves were absent. Dermatoscopy revealed abnormal vessel patterns in the form of corkscrew-shaped, tortuous blood vessels and microthrombi in the ectatic vessels alongside small ulcers (▶ Figs. 4–6).

Laboratory diagnosis

Since a vascular genesis of the clinical changes was still suspected, a skin biopsy was taken to start with and, since the dermatoscopic findings were strongly suggestive of vasculopathy, the serological investigations were then widened to include an extensive antibody profile. This revealed a high titre for the beta-2 glycoprotein IgA subtype.

Histological picture

The histological picture was consistent with vasculopathy affecting the small vessels and excluded vasculitis as the cause. Below a normally constructed epidermis, there were groups of small thick-walled vessels (post-capillary venules), some of which showed thrombosis, alongside extravasated red blood cells (▶ Fig. 7). There was no perivascular infiltrate, as classically occurs in vasculitis.

Treatment and subsequent course of the disease

Treatment was initiated with aspirin 100 mg daily as guideline-conforming platelet aggregation inhibiting therapy. This led to a complete healing of the initially present ulcers. Results remained stable on follow-up for up to one year after the start of treatment. In July 2017, the patient presented

with a renewed episode. Once again, the clinical picture showed disseminated small ulcers in the region of the medial malleolus. As laboratory studies revealed a renewed high titre of beta-2 glycoprotein IgA, we introduced systemic chloroquine phosphate 250 mg/day in parallel to the existing platelet aggregation inhibitor. When a further increase in symptoms occurred in March 2018, the systemic treatment with aspirin was increased from 100 mg to 300 mg daily. Under this treatment the findings stabilised, no new ulcers developed and the systemic treatment with chloroquine phosphate could be reduced to 50 mg daily and aspirin to 100 mg daily.

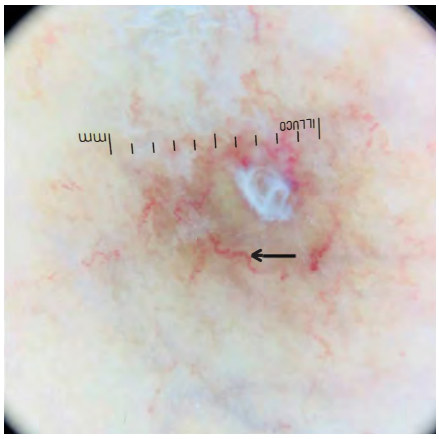

Fig. 4 Dermatoscopy: a small ulcer with a cream coating surrounded by corkscrew-shaped vessels (arrow)

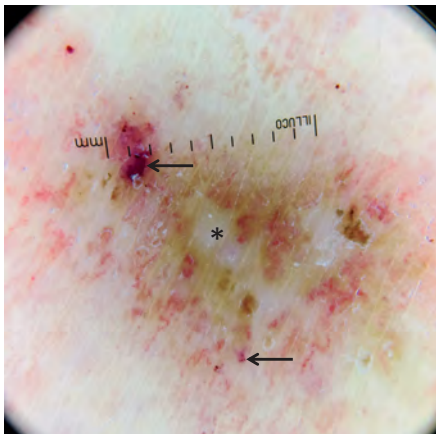

Fig. 5 Dermatoscopy: healed porcelain-coloured areas (*) surrounded by pigment deposits and ectatic, sometimes freshly thrombosed vessels (arrow)

Discussion

For several years there has been disagreement in clinical research about the importance of IgA antibodies in antiphospholipid syndrome. According to the recommendation of the consensus paper of the 14th International Congress on Antiphospholipid Syndrome, IgA subtype antiphospholipid antibodies should be measured if there is a strong clinical suspicion of an antiphospholipid syndrome but negative titres of IgM and IgG antiphospholipid antibodies (8).

In our case, the typical prepartal complications were not present. This could be because, unlike IgG, IgA does not cross the placenta. Nevertheless, the clinical appearance of disseminated tiny ulcers in the skin, together with pre-existing atypical patterns of vessels in the form of teleangiectasia, did not allow many differential diagnoses. In addition to the group of highly inflammatory forms of small-vessel vasculitis, blood vessel disease also includes coagulopathies.

These can be quickly differentiated by histology. The antiphospholipid syndrome, which is one of the vasculopathies, causes microthrombi in the dermal vessels, and the resulting hypoperfusion causes tissue death of the associated skin segment. In contrast, by inducing inflammatory changes of the vessel walls, vasculitis induces extravasation of red blood cells through the increased tissue permeability and the typical palpable purpura. Inflammation of the vessels leads to secondary occlusion of the lumina and thus to skin necrosis.

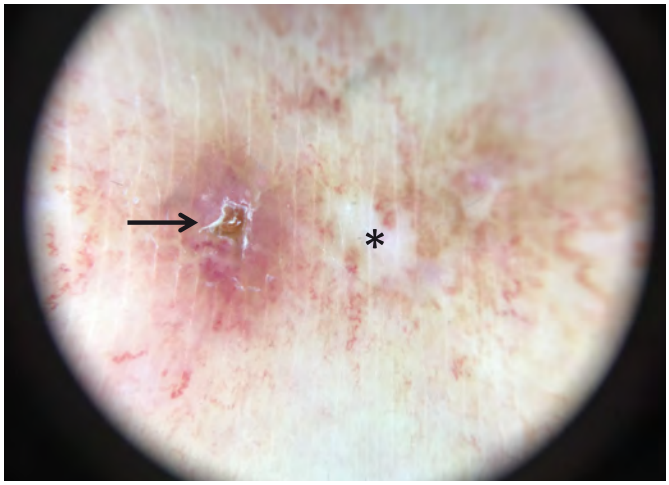

Fig. 6 Dermatoscopy: healed porcelain-coloured areas (*) surrounded by ectatic, corkscrew-shaped vessels and a small active ulcer (arrow)

Tab. 1 Extension of the serological investigations to supplementary antibody profiles: this showed a high titre for the beta-2 glycoprotein IgA subtype.

Antibody	Titre
Cardiolipin IgM	<2Mpl/ml (normal range <2Mpl/ml)
Cardiolipin IgG	2.1Gpl/ml (normal range <12Gpl/ml)
Beta-2 glycoprotein IgM	5 RU/ml (normal range <20)
Beta-2 glycoprotein IgG	<2 RU/ml (normal range <20)
Beta-2 glycoprotein IgA	>200 RU/ml (normal range <20)

Similar to IgA-positive vasculitis that is sometimes limited only to the skin (9), the IgA vasculopathy also only affected the skin in our patient. Therefore certain parallels can be drawn between these two IgA immune complex diseases.

In the case of IgA-positive leukocytoclastic vasculitis (Schoenlein-Henoch purpura), the reduced activity of beta1,3 galactosyltransferase in the peripheral B-cells leads to abnormal glycosylation of IgA-1. The pathological IgA causes a reduced immune defence at the mucous membranes. This leads to the formation of large immune complexes in the blood (10) that, in the case of antiphospholipid syndrome, can result in occlusions in the small vessels of the dermis.

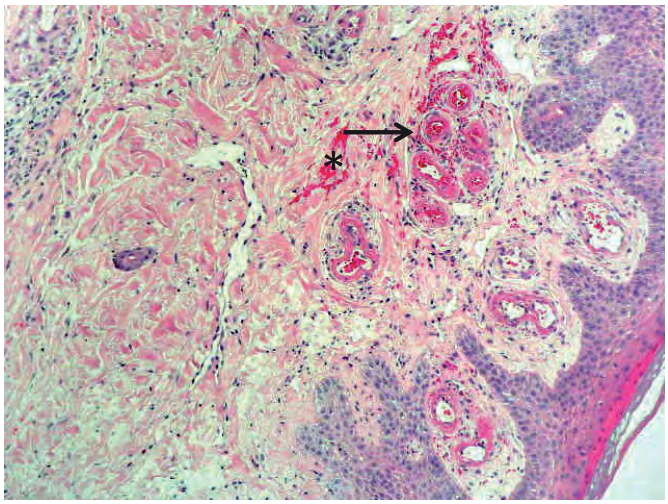

Fig. 7
HE stain, 10x. Histological picture of vasculopathy: many subepidermal small vessels, arranged in groups (arrow) (that correspond to the clinical correlate of the corkscrew-like pattern) with hyaline-thickened walls with no perivascular infiltrate, in addition there are extravasated red blood cells (*)

Summary

In the case of recurrent and disseminated ulcers of unknown cause – particularly on the lower extremities – and negative primary autoimmunological serology, the possibility of the rare IgA antiphospholipid syndrome should be considered. In additional to appropriately expanded laboratory tests, a biopsy is often helpful.

Conflict of interest

The authors declare that there are no conflicts of interest.

Ethical guidelines

No studies in humans or animals were conducted for the manuscript.

References

1. Hughes JP, Stovin PGI. Segmental pulmonary artery aneurysms with peripheral venous thrombosis. Br J Dis Chest 1959; 53: 19–27. doi:10.1016/S0007–0971(59)80106–6
2. Cervera R. Antiphospholipid sydrome. In: Thrombosis Research 2017; 151: 43–S47. DOI: 10.2016/S0049–3848(17)30066-X.
3. Gómez-Puerta JA, Cervera R. Diagnosis and classification of the antiphospholipid syndrome. In: Journal of autoimmunity 2014; 48–49: 20–25. DOI:10.1016/j.jaut.2014.01.006.
4. Cervera R, Khamashta MA, Shoenfeld Y, Camps MT, Jacobsen S, Kiss E et al. Morbidity and mortality in the antiphospholipid syndrome during a 5-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2009; 68: 1428–1432.
5. Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, de Ramón E et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2015; 74: 1011–1018.
6. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999; 42: 1309–1311.
7. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006; 4: 295–306.
8. 14th International Congress on Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome Treatment Trends Doruk Erkan a, Cassyanne L. Aguiar a, Danieli Andrade b, Hannah Cohen c,d, Maria J. Cuadrado e, Adriana Danowski f, Roger A. Levy g, Thomas L. Ortel h, Anisur Rahman c,d, Jane E. Salmon a, Maria G. Tektonidou i, Rohan Willis j, Michael D. Lockshin a
9. Sunderkötter C, Pappelbaum K, Ehrchen J. Hautarzt 2015; 66: 589. https://doi.org/10.1007/s00105–015–3661–6
10. Davin J-C. Henoch-Schonlein purpura nephritis. Pathophysiology, treatment, and future strategy. Clinical journal of the American Society of Nephrology, CJASN 2011; 6 (3): 679–689. DOI: 10.2215/CJN.06710810.