Eosinophilia and Antiphospholipid Antibodies: Double Thrombogenic Hits? A New Case with a Systematic Review

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Abstract
Peripheral blood eosinophilia (PBE) may be associated with the development of thrombosis and this holds true also for transient PBE though in the latter case the likelihood of thrombosis may not be as high as for long standing PBE. The co-existence of transient PBE with other pro-coagulant factors may precipitate thrombosis in some patients. We report a young gentleman with PBE of unknown cause who developed thrombosis at the peak of his transient PBE and was later found to have antiphospholipid antibodies. We performed a systematic review to evaluate how often the two conditions co-existed, their clinical expression and their management.

Keywords: Peripheral blood eosinophilia; antiphospholipid antibody

Introduction
In the last decade there has been a resurgence of interest in the development of thrombosis associated with peripheral blood eosinophilia (PBE), regardless of the background condition leading to PBE and of the chronic [1,2] or transient nature of the PBE [3,4]. An early series on the hypereosinophilic syndrome (HES) where PBE was persistent underscored the elevated frequency of thrombosis often recurrent despite adequate warfarin or heparin anticoagulation [5]. But even transient PBE by itself can be a strong enough drive for the development of thrombosis [3,4]: herein describe a case of venous thromboembolism (VTE) developing during a transient PBE followed by the discovery of antiphospholipid antibodies (aPL) that has led to the subsequent diagnosis of antiphospholipid syndrome (APS). The case prompted us to perform a systemic review to verify how frequently PBE and aPL co-exist and whether the co-existence informed further on the thrombogenic pathways of both conditions and its management.

Case Description
A 34-year-old gentleman was referred to casualty by his general practitioner in May 2014 for a swollen left leg preceded in the previous two weeks by a diarrhoeal illness. His Well’s score was 1 [6] but a D-dimer was raised at 1087 ng/ml and a Doppler ultrasound showed a 4 cm long popliteal vein occlusion. No history of trauma or new drug intake was reported. There was neither personal nor family history of venous thromboembolism (VTE) developing during a transient PBE followed by the discovery of antiphospholipid antibodies (aPL) that has led to the subsequent diagnosis of antiphospholipid syndrome (APS). The case prompted us to perform a systemic review to verify how frequently PBE and aPL co-exist and whether the co-existence informed further on the thrombogenic pathways of both conditions and its management.

Results
The systematic review yielded 12 papers dealing with 12 cases [7-18] of which 10 presented with vascular occlusions and two did [17,18] not but we included them to verify the outcome of PBE and aPL (Table 1). Of the total 11 cases (including ours) presenting with vascular occlusions [7-16] three did not mentioned the eosinophil count [12-14] and 6 did not report values of aPL testing (either immune and clotting assays) [11-14,16]. Repeat assays to confirm the initial presence of aPL was performed in one case only [7] and post-treatment in four cases only [10,15,18]. One patient had mild PBE (0.5 to 5.0 × 109/L) [17], still positive at 16 months review (36 GPL and 42 U/ml respectively) but PBE never reappeared.

Systematic Literature Review
PRJA, MM and AA searched Medline and Embase from inception to December 2015 by using the terms peripheral blood eosinophilia, anticardiolipin, antiphospholipid and lupus anticoagulant for suitable articles. Inclusion criteria were articles written in English, French, Spanish, Italian and Portuguese. Exclusion criteria were articles not written in the languages mentioned above and articles showing data on tissue and not peripheral blood eosinophilia.

The search yielded 63 articles, after elimination of duplicates 55 were screened and 4 removed leaving 13 articles eligible for evaluation: of these one was excluded because it was in Polish and did not contain relevant information. We also checked the reference list of retrieved papers to look for possible references that we might have missed. Any discrepancy was resolved by consensus.

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three patients had moderate PBE (1.51 to 5.0 × 10^9/L) [10,11] and the remaining had severe PBE [7-9,15,16,18]. With regards to aPL three cases had low titres [15,16] in association with a LA in one case only (ours), two cases had medium titres [7,9] with no mention of LA, and two cases had high titres [8,10]; three cases reported a positive LA alone [11,16,18].

With regards to thrombosis, vessel occlusions occurred on the venous side (deep vein thrombosis and pulmonary embolism) in 6 cases [8,10,11,13,16], in association with ischaemic stroke in two cases [8,10]; arterial occlusions occurred in isolation in three cases [7,9,14] and with left ventricular thrombus in one case [15].

### Discussion

PBE is associated with the occurrence of thrombosis in different settings, including chronic filariasis [2], HES [5] and Churg-Strauss syndrome [1] where PBE may be more persistent, though the chance of developing thrombosis may occur also in patients with PBE of short term duration [3,4]. It is unclear whether a threshold level of PBE exists at which vascular occlusions develop, but this risk may be higher if another thrombogenic stimulus is present as in our patient who developed DVT on the day of maximal PBE and who was found to have a LA shortly afterwards. The systematic review identified another two cases where PBE and aPL coexisted: in ten the co-existence was associated with different types of vascular occlusions mostly deep vein thrombosis and ischemic stroke.

Interestingly APS and PBE share overlapping pathways that may lead to vessel occlusion. The thrombogenic potential of aPL is well established: depressed fibrinolysis, inhibition of natural anticoagulants, enhanced tissue factor expression on monocytes and endothelial cells all contribute to increased thrombin generation, that in turn favours platelet activation, thromboxane release, fibrin polymerization with vessel occlusion a possible consequence [19]. The thrombogenic potential of the eosinophil and its granules is less known but involves inhibition of natural anticoagulant activity, enhanced tissue factor expression on monocytes and eosinophils, increased thromboxane release and thrombin generation [1].

In the cases described it is difficult to tease out which was the relative pro-thrombotic contribution of the two conditions; certainly vascular occlusions developed regardless of the background condition leading to PBE though in two cases vasculitis may have contributed to vessel damage adding to the thrombotic risk [7,14]. Of the reported cases, PBE was moderate to severe in most: indeed the patient with severe PBE and the highest aCL suffered multiple occlusive events [8] whereas the patient with mild PBE and low aCL did not suffer thrombosis [17]. Other cases cited only the LA without its strength and had medium-low titres aCL suggesting that PBE may have been more relevant than aPL in thrombosis development. The only other patient with high titre aCL was affected by hepatic fascioliasis and treatment of the fluke led to a fall in the aCL titre [10].

PBE and APS may also be associated with recurrent thrombosis despite adequate anticoagulation [5,20]. This did not occur in any patient of the review because various treatments decreased PBE and minimised this aspect of the thrombotic risk whereas aPL rarely decrease even after targeted treatment [21]. Only four authors reported the fate of aPL post treatment [10,15,16]: IgG aCL disappeared or improved in the two cases of hepatic fascioliasis [10,15] suggesting a reactive nature for the aPL in this disease and in the patient with ALL [18].

The systematic review has described the rare association of PBE with aPL that share an overlapping pathogenesis leading to vascular occlusion in twelve patients. Limitations of the systematic review are: 1) the lack of prevalence data in the literature on the association between aPL and PBE; 2) the need to treat the background diseases justified a single aPL measurement but even after treatment a repeat aPL was re-checked only in four reports [10,15,18]. It is the responsibility of reviewers and editors alike to take these shortcomings into account and prevent the publication of poorly documented cases that will contribute little to the understanding of this rare co-existence. The purpose of this review is to highlight the thrombogenic potential of PBE across the

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### Table 1: Clinical and laboratory features of cases with coexistent peripheral blood eosinophilia and antiphospholipid antibodies.

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Diagnosis</th>
<th>PBE</th>
<th>aPL</th>
<th>LA</th>
<th>Occlusion type</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>34/M</td>
<td>APS</td>
<td>2.77</td>
<td>29</td>
<td></td>
<td>DRVVT 2.59</td>
<td>DVT</td>
<td>W</td>
<td>Improved DRVT 1.84</td>
</tr>
<tr>
<td>46/F</td>
<td>CSS/APS</td>
<td>8.64</td>
<td></td>
<td>qβ</td>
<td>GPI 50/82 IU/L</td>
<td>IS</td>
<td>IV MP, oral P, C, W</td>
<td>Improved NA</td>
</tr>
<tr>
<td>15/M</td>
<td>EMF/SLE</td>
<td>6.4</td>
<td>500</td>
<td></td>
<td>DVT/PE, IS, SI</td>
<td>Oral P, OHCQ, W</td>
<td>Improved PBE improved</td>
<td>[8]</td>
</tr>
<tr>
<td>34/F</td>
<td>HES/SLE</td>
<td>7.5</td>
<td>50</td>
<td>IS</td>
<td>(lacunar), EMF</td>
<td>IV MP/oral P, AZP W</td>
<td>Improved PBE improved</td>
<td>[9]</td>
</tr>
<tr>
<td>50/F</td>
<td>APS</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>DVT, EMF</td>
<td>NA</td>
<td>NA NA</td>
<td>PBE improved</td>
</tr>
<tr>
<td>8.5/M</td>
<td>PAN</td>
<td>NA</td>
<td>+ve</td>
<td></td>
<td>Finger amputation</td>
<td>Oral P, ASA</td>
<td>Recurrence</td>
<td>NA</td>
</tr>
<tr>
<td>22/F</td>
<td>HES</td>
<td>16.8</td>
<td></td>
<td>+ve</td>
<td>PE/infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/F</td>
<td>ALL</td>
<td>16</td>
<td></td>
<td>+ve</td>
<td>DRVVT +ve</td>
<td>Chorea</td>
<td>Chemotherapy Improved PBE improved</td>
<td>DRVVT +ve</td>
</tr>
<tr>
<td>68/F</td>
<td>FH</td>
<td>4.8</td>
<td>120</td>
<td>+ve</td>
<td>DVT/IS</td>
<td>Triclabendazole</td>
<td>Improved PBE improved</td>
<td>IgG aCL</td>
</tr>
<tr>
<td>60/M</td>
<td>Aspergillosis</td>
<td>4.4</td>
<td></td>
<td>+ve</td>
<td>DVT</td>
<td>H, oral P</td>
<td>Improved PBE</td>
<td></td>
</tr>
<tr>
<td>79/F</td>
<td>Ascariasis</td>
<td>yes</td>
<td></td>
<td>+ve</td>
<td>Skin vessels</td>
<td>Ivermectin</td>
<td>Improved PBE</td>
<td>NA</td>
</tr>
<tr>
<td>40/F</td>
<td>FH</td>
<td>7.6</td>
<td>40</td>
<td></td>
<td>IS/LVT</td>
<td>W, oral P, dehydrocortisone</td>
<td>Improved PBE improved</td>
<td>IgG aCL 29</td>
</tr>
<tr>
<td>36/F</td>
<td>Enteritis/SLE</td>
<td>7.2</td>
<td>23.8</td>
<td></td>
<td>None</td>
<td>IV MP</td>
<td>Improved</td>
<td></td>
</tr>
</tbody>
</table>

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different spectrum of conditions where it appears. It is hoped that future cases are better documented, that centres dealing with eosinophilic disorders measure aPL as part of their routine investigations, assess prevalence and patterns of vascular occlusions if they occur to inform the medical community of the thrombogenic potential of the two disorders.

References


