

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 likely hood 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. Full blood count revealed eosinophilia at $2.77 \times 10^9/L$ that prompted a search for ova and parasites in the stool on three occasions with negative results whereas c-ANCA and p-ANCA were negative. Chemistries were all normal. ANA, C-ANCA, P-ANCA were all negative. A chest x-ray and total body CT scan done to exclude malignancy, infection and autoimmune diseases were normal. An echocardiogram was also normal. The eosinophilia settled spontaneously after two weeks. A thrombophilia screen showed an increased dilute Russell viper venom time ratio (DRVVTr) at 2.59 that corrected to 1.09 with the platelet neutralisation procedure and positive IgG anticardiolipin antibodies (aCL) at 29 GPL. After six months the DRVVTr decreased spontaneously to 1.84, IgG aCL was 28 GPL and D-dimer was elevated at 602 ng/ml. It was decided to continue anticoagulation indefinitely given the diagnosis of primary antiphospholipid syndrome. His IgG aCL and anti β_2 glycoprotein-I are

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.

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 mention 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 $5.0 \times 10^9/L$) [17],

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Age/sex	Diagnosis	PBE 10x9/L	aPL		LA	Occlusion type	Treatment	Outcome		Ref
			IgG aCL GPL	IgM aCL MPL				Clinical	Laboratory	
34/M	APS	2.77	29		DRVVTr 2.59	DVT	W	Improved	DRVVT 1.84	Our
46/F	CSS/APS	8.64		$\alpha\beta_2$ GPI 56/62 IU/L		IS	IV MP, oral P, C, W	Improved	NA	[7]
15/M	EMF/SLE	6.4		500		DVT/PE, IS, SI	Oral P, OHCQ, W	Improved	PBE improved	[8]
34/F	HES/SLE	7.5	50			IS (lacunar), EMF	IV MP/oral P, AZP W	Improved	PBE improved	[9]
50/F	APS	NA	NA		NA	DVT, EMF	NA	NA	NA	[13]
8.5/M	PAN	NA	+ve			Finger amputation	Oral P, ASA	Recurrence	NA	[14]
22/F	HES	16.8			+ve	PE/infarction				[16]
5/F	ALL	16			DRVVT +ve	Chorea	Chemotherapy	Improved	PBE improved DRVVT -ve	[18]
68/F	FH	4.8	120		+ve	DVT/IS	Triclabendazole	Improved	PBE improved IgG aCL -ve	[10]
60/M	Aspergillosis	4.4			+ve	DVT	H, oral P	Improved	PBE improved	[11]
79/F	Ascariasis	yes			+ve	Skin vessels	Ivermectin	Improved	NA	[12]
40/F	FH	7.6	40			IS/LVT	W, oral P, dehydroemetin	Improved	PBE improved IgG aCL 29	[15]
36/F	Enteritis/SLE	0.72	23.8			None	IV MP		Improved	[17]

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

three patients had moderate PBE (1.51 to $5.0 \times 10^9/L$) [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 twelve 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 to perform a meta-analysis; 2) poorly informative case studies from the laboratory point of view. In fact type and values of aPL were not always reported and measured only once in most cases, preventing the diagnosis of APS that requires the persistence of the aPL at least three months apart [22].

On other hand, 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

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

1. Ames PR, Margaglione M, Mackie S, Alves JD (2010) Eosinophilia and thrombophilia in Churg Strauss syndrome: a clinical and pathogenetic overview. *Clin Appl Thromb Hemost* 16: 628-636.
2. Ames PR, Aloj G, Gentile F (2011) Eosinophilia and thrombosis in parasitic diseases: an overview. *Clin Appl Thromb Hemost* 17: 33-38.
3. Ames PR (2011) Recurrent abdominal thrombosis despite heparin thromboprophylaxis in a patient with transient eosinophilia. *Clin Appl Thromb Hemost* 17: 229-231.
4. Sano H, Fukuoka T, Maruyama H, Hayashi T, Tanahashi N (2014) Cerebral sinovenous thrombosis in a patient with transient eosinophilia. *Intern Med* 53: 2139-2142.
5. Spry CJ, Davies J, Tai PC, Olsen EG, Oakley CM, et al. (1983) Clinical features of fifteen patients with the hypereosinophilic syndrome. *Q J Med* 52: 1-22.
6. Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, et al. (2003) Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med* 349: 1227-1235.
7. Paroli M, Polidoro A, Romano S, Accapezzato D (2012) Churg-Strauss syndrome associated with antiphospholipid antibodies in a patient with recurrent myocardial and cerebral ischemia. *Int Med Case Rep J* 5: 79-81.
8. Aydođdu S, Uçar O, Cetin M (2010) A case of systemic lupus erythematosus presenting with hypereosinophilia and Loeffler endocarditis. *Acta Cardiol* 65: 571-573.
9. Habibagahi Z, Ali Nazarinia M, Aflaki E, Ali Ostovan M, Hadi Bagheri M (2009) Systemic lupus erythematosus and hyper-eosinophilic syndrome: an unusual association. *West Indian Med J* 58: 69-71.
10. Linares P, Fernandez-Gundin MJ, Vivas S, Suarez P, Olcoz JL (2006) Unusual thrombotic manifestations secondary to antiphospholipid syndrome and hepatic fascioliasis. *J Infect* 52: 75-76.
11. Niitsuma T, Nukaga M, Izawa A, Tsuyuguchi M, Tsuboi N, et al. (2003) Antiphospholipid syndrome during allergic bronchopulmonary aspergillosis. *Allergy* 58: 454-455.
12. Estève E, Maitre F, Legac E (2001) [Vascular purpura in a patient with severe sarcoptic acariasis]. *Ann Dermatol Venereol* 128: 911-914.
13. Azeem T, Vassallo M, Samani NJ (2000) Images in cardiology. Endomyocardial fibrosis associated with antiphospholipid syndrome. *Heart* 84: 156.
14. Pereira BA, Silva NA, Ximenes AC, Alvarenga SL, Barbosa VS (1995) Cutaneous polyarteritis nodosa in a child with positive antiphospholipid and P-ANCA. *Scand J Rheumatol* 24: 386-388.
15. Francès C, Piette JC, Saada V, Papo T, Wechsler B, et al. (1994) Multiple subungual splinter hemorrhages in the antiphospholipid syndrome: a report of five cases and review of the literature. *Lupus* 3: 123-128.
16. Koike R, Yoshida S, Takahashi H (1991) [A case of idiopathic hypereosinophilic syndrome (HES) complicated by pulmonary infarction]. *Arerugi* 40: 1232-1238.
17. Jaimes-Hernandez J, Aranda-Peirera P, Melendez-Mercado CI (2009) Eosinophilic enteritis in association with systemic lupus erythematosus. *Lupus* 18: 452-456.
18. Schiff DE, Ortega JA (1992) Chorea, eosinophilia, and lupus anticoagulant associated with acute lymphoblastic leukemia. *Pediatr Neurol* 8: 466-468.
19. Du VX, Kelchtermans H, de Groot PG, de Laat B (2013) From antibody to clinical phenotype, the black box of the antiphospholipid syndrome: pathogenic mechanisms of the antiphospholipid syndrome. *Thromb Res* 132: 319-326.
20. Lim W (2014) Thrombotic risk in the antiphospholipid syndrome. *Semin Thromb Hemost* 40: 741-746.
21. Galli M (2013) Treatment of the antiphospholipid syndrome. *Auto Immun Highlights* 5: 1-7.
22. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, et al. (2006) International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 4: 295-306.