Venous thromboembolism with concurrent pulmonary haemorrhage in systemic vasculitis

Erika De Sousa, Rona Smith, Afzal Chaudhry, Lisa Willcocks and David Jayne

Vasculitis and Lupus Clinic, Addenbrooke’s Hospital, Cambridge, UK

Correspondence and offprint requests to: Erika De Sousa; E-mail: erikades4@gmail.com

Abstract

Background. Pulmonary haemorrhage (PH) is a serious manifestation of systemic vasculitis with high mortality rates yet vasculitis is associated with an increased prevalence of venous thromboembolism (VTE). The concurrent presentation of severe PH and VTE poses a challenge in terms of therapeutic management.

Methods. This is a retrospective case review of the clinical manifestations and response to treatment in vasculitis patients presenting with concurrent pulmonary haemorrhage and VTE (pulmonary embolism and/or deep venous thrombosis).

Results. Of 35 patients with severe PH due to systemic vasculitis, 7 (20%) had concurrent VTE. The most common cause was anti-neutrophil cytoplasm antibody-associated vasculitis, followed by anti-glomerular basement membrane disease. Vasculitis responded to conventional therapies and VTE treatment with anticoagulation was uncomplicated in five of six cases. In one case, anticoagulation precipitated the PH and another was not anticoagulated and developed recurrent VTE. All patients survived without further complications after a mean follow-up of 46 months (3–98).

Conclusions. Concurrent VTE occurred in one-fifth of cases with severe PH due to vasculitis. Management of VTE with anticoagulation was effective but led to pulmonary haemorrhage in one patient.

Keywords: ANCA; deep venous thrombosis; pulmonary embolism; pulmonary haemorrhage; vasculitis

Introduction

Pulmonary haemorrhage (PH) is a potentially life-threatening manifestation of systemic vasculitis and requires aggressive treatment. The most common causes are anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis (AAV) and antiglomerular basement membrane (GBM) disease [1, 2]. Venous thromboembolism (VTE) is a frequent complication of systemic vasculitis that poses a challenge in therapeutic management when it occurs in patients with active haemorrhage [3, 4]. We describe the frequency and management of this presentation in a cohort of patients with systemic vasculitis.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Diagnosis and organ involvement</th>
<th>Previous VTE</th>
<th>Previous treatment</th>
<th>VTE</th>
<th>Presentation</th>
<th>Requirement for supportive care</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48 (F)</td>
<td>AAV, renal and ENT</td>
<td>PE 12 years prior, AC for 6 months</td>
<td>No</td>
<td>PE</td>
<td>Simultaneous PH and PE</td>
<td>None</td>
<td>Alive, new PE after 1 month, long-term AC</td>
</tr>
<tr>
<td>2</td>
<td>16 (M)</td>
<td>Anti-GBM disease, lung</td>
<td>No</td>
<td>No</td>
<td>Lower limb DVT, Multiple PE's</td>
<td>PE's and DVT 2 weeks after PH</td>
<td>None</td>
<td>Alive, remains on AC</td>
</tr>
<tr>
<td>3</td>
<td>58 (F)</td>
<td>Anti-synthetase syndrome (pulmonary fibrosis and polymyositis)</td>
<td>DVT 6 years prior AC for 6 months</td>
<td>Steroids, AZA, MTX, CYC, MMF</td>
<td>Lower limb DVT, Multiple PE's</td>
<td>Simultaneous PH and VTE</td>
<td>None</td>
<td>Alive, long-term AC, pulmonary fibrosis</td>
</tr>
<tr>
<td>4</td>
<td>58 (F)</td>
<td>Anti-GBM disease, renal</td>
<td>No</td>
<td>No</td>
<td>Lower limb DVT</td>
<td>DVT presented 1 week after partial resolution of PH</td>
<td>Required dialysis, ITU admittance for non-invasive ventilation</td>
<td>Alive, late haemorrhagic complications related to AC, end-stage renal disease</td>
</tr>
<tr>
<td>5</td>
<td>19 (F)</td>
<td>AAV, renal and ENT</td>
<td>No</td>
<td>No</td>
<td>Upper limb DVT, Multiple PE's</td>
<td>Simultaneous PH and VTE</td>
<td>ITU admittance for mechanical ventilation, miscarriage during stay, acute kidney injury</td>
<td>Alive, AC stopped after 6 months</td>
</tr>
<tr>
<td>6</td>
<td>61 (M)</td>
<td>AAV; dermatomyositis with pulmonary fibrosis, renal, CNS and ENT</td>
<td>No</td>
<td>Steroids, AZA, MMF</td>
<td>Multiple PE's</td>
<td>PE diagnosed 2 weeks prior to PH</td>
<td>Required dialysis, ITU admittance for mechanical ventilation, severe sepsis</td>
<td>Alive, AC stopped after 6 months, pulmonary fibrosis</td>
</tr>
<tr>
<td>7</td>
<td>45 (M)</td>
<td>AAV, Renal and ENT</td>
<td>No</td>
<td>No</td>
<td>Lower limb DVT, Multiple PE's</td>
<td>VTE presented 1 week after partial resolution of PH</td>
<td>Acute kidney injury</td>
<td>Alive, long-term AC, chronic kidney disease stage 3</td>
</tr>
</tbody>
</table>

Patient demographics, clinical manifestations and outcomes. M, male; F, female; VTE, venous thromboembolic event; PE, pulmonary embolism; AC, anticoagulation; ENT, ear nose and throat; CNS, central nervous system; MMF, mycophenolate mofetil; AZA, azathioprine; CYC, cyclophosphamide; MXT, methotrexate.

4358 E. De Sousa et al.
are summarized in Table 2. No patient had coagulopathy or critical thrombocytopenia (<50,000 cells/mm³).

Therapy of vasculitis is described in Table 3 with four receiving plasma exchange (PEx). Anticoagulation was started after the VTE diagnosis in five and after a delay of 7 days in one (Table 3). One case did not receive anticoagulation and an inferior vena caval (IVC) filter was inserted. One case developed PH 2 weeks after initiation anticoagulation for VTE; this case received PEx for PH and anticoagulation was maintained with low-molecular-weight heparin (LMWH). Four had an IVC filter inserted including the case with delayed anticoagulation.

All patients survived after a median follow-up of 46 months (range 3–98). A subsequent PE occurred in the patient who did not receive anticoagulation and was later treated with LMWH for 6 months. There were no further episodes of haemorrhage. Long-term anticoagulation was prescribed only for repeated VTE. Pulmonary fibrosis present at the time of vasculitis diagnosis in two was not observed in the others during follow-up.

Discussion

The frequency of PH in AAV and anti-GBM disease is 24 and 50%, respectively [5, 6]. There is an increased risk of VTE in AAV patients with a reported incidence of 7.0 per 100 person-years in granulomatosis with polyangiitis (Wegener’s) associated with active disease [7]. There is one reported case of concurrent VTE and PH in vasculitis where anticoagulation led to worsening of PH [4].

We found a 20% incidence of VTE in severe PH indicating the clinical importance of this association. The majority were initial disease presentations that responded
appropriately to conventional therapies including PEx. No worsening of PH occurred in five of six patients anticoagulated preventing further VTEs, except in one case where anticoagulation precipitated the PH, so the benefits of anticoagulation must be balanced against the potential risk of haemorrhagic complications.

The higher incidence of VTE in AA V is not related to the presence of classical risk factors [8–10]. Inflammation of the vessel wall, caused by local ANCA-induced neutrophil activation, is a potential mechanism [11, 12]. The recent identification of autoantibodies to plasminogen to tissue plasminogen activator in AA V, with in vitro potential to retard fibrinolysis, may also explain the increased thrombotic risk [13].

The combination of conventional immunomodulatory therapy with anticoagulation was effective for both PH and VTE pathologies, leading to haemorrhagic complications in only one case. Intracaval filters did not obviate the need for anticoagulation but are an option if anticoagulation is delayed. Long term outcomes were good in all patients.

Acknowledgements. This study was supported by the Cambridge Biomedical Research Centre.

Conflict of interest statement. None declared.


References

Investigating FGF-23 concentrations and its relationship with declining renal function in paediatric patients with pre-dialysis CKD Stages 3–5

Manish D. Sinha1, Charles Turner2, R. N. Dalton2, Pernille Rasmussen1, Simon Waller1, Caroline J. Booth1 and David J. Goldsmith3

1Department of Paediatric Nephrology, Evelina Children’s Hospital, Guy’s and St Thomas’ NHS Foundation Trust, London, UK, 2WellChild Laboratory, King’s College London, Guy’s and St Thomas’ NHS Foundation Trust, London, UK and 3Department of Nephrology, Guy’s and St Thomas’ NHS Foundation Trust, London, UK

Correspondence and offprint requests to: Manish D. Sinha; E-mail: manish.sinha@gstt.nhs.uk

Abstract

Background. The aims of our study were to investigate (i) the prevalence of elevated fibroblast growth factor-23 (FGF-23), (ii) the relationship between FGF-23 concentrations and level of renal dysfunction and (iii) the main determinants of elevation of FGF-23 concentration in children with pre-dialysis chronic kidney disease (CKD) Stages 3–5.

Methods. In this single-centre prospective observational study, 71 children with pre-dialysis CKD Stages 3–5, aged 11.9 ± 3.1 years, had FGF-23 levels measured. Anthropometry and routine laboratory investigations were measured.

Results. Fourteen (19.7%) patients had normal FGF-23 concentrations defined as <50 ng/L. FGF-23 [median (interquartile range)] concentrations were 78.7 (55.6–137.6) ng/L and following log transformation normalized data with log FGF-23 [mean (SD)] values of 1.96 ± 0.4 ng/L. Log FGF-23 concentrations had a negative reciprocal relationship with estimated glomerular filtration rate (eGFR) (P < 0.0001) and 1.25 vitamin D3 levels (P = 0.01) and a positive relationship with phosphate (P = 0.03) and percent fractional excretion of phosphate (P = 0.01) but not with log-intact parathyroid hormone (PTH) (P = 0.22). Multiple linear regression demonstrated a strong relationship between log FGF-23 and eGFR only.

Conclusions. Elevated FGF-23 concentrations were observed in the majority of a carefully managed cohort of children with non-dialysis CKD with a dominant effect on FGF-23 concentrations with glomerular filtration rate (GFR). These data allow the potential confounding effects of PTH and phosphate elevation with declining GFR to be removed, leaving a clearer picture of the FGF-23—GFR relationship.

Keywords: children; mineral bone disease; phosphate control

Introduction

Fibroblast growth factor-23 (FGF-23) is one of the most important regulators of blood phosphate levels. It is...