Incidence of fatal venous thromboembolism in antineutrophil cytoplasmic antibody-associated vasculitis

Incidência de tromboembolismo venoso fatal em vasculite associada a anticorpo anticitoplasma de neutrófilos

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To the Editor:

Here, we report the case of a patient with fatal venous thromboembolism (VTE) during active antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. This report is the first of its kind to be published in an English-language journal dedicated to pulmonology. In addition, we estimated, for the first time, the VTE-related mortality rate in patients with ANCA-associated vasculitis.

Classically, the onset of hemoptysis and dyspnea in patients with ANCA-associated vasculitis promptly leads physicians to consider diffuse alveolar hemorrhage (DAH). However, there is increasing evidence that the risk of VTE is high in ANCA-associated vasculitis, especially during the active phase.[1-6] In addition, VTE can manifest as hemoptysis and dyspnea in any patient, including those with ANCA-associated vasculitis.

In July of 2010, we conducted a search of the PubMed database, using the terms ((anca AND vasculitis) OR ((Wegener's OR Wegeners OR Wegener) AND granulomatosis)) AND (embolism OR embolic OR thromboembolism OR thromboembolic) and limiting the search to the last 30 years. We identified only three articles published in English-language journals dedicated to pulmonology.[7-9] We found it intriguing that none of these articles specifically discussed the association between ANCA-associated vasculitis and VTE.

We treated a 61-year-old woman who, 24 months prior, had been diagnosed with ANCA-associated vasculitis (specifically Wegener's granulomatosis, with nasal inflammation, abnormal chest radiography, and granulomatous inflammation on lung biopsy at diagnosis) and had been in remission for 18 months. She presented to our emergency room with a seven-day history of left-leg edema and purpura on both legs, as well as dyspnea and hemoptysis for three days. She had been under treatment with prednisone (10 mg/day) and sulfamethoxazole for the last 6 months. Physical examination revealed dyspnea, left-leg edema, and palpable purpura (Figure 1a). Her SpO_2 was 83% on room air. The abnormal results of the ancillary tests were elevated erythrocyte sedimentation rate and positivity for cytoplasmic-ANCA, together with pulmonary embolism (PE), pulmonary consolidation consistent with PE-related pulmonary infarction, and deep venous thrombosis (DVT), as shown in Figure 1b. Consequently, the patient received a diagnosis of active ANCA-associated vasculitis with VTE (without DAH). She was started on enoxaparin (1 mg/kg twice a day), prednisone (60 mg/day), oral cyclophosphamide, sulfamethoxazole, and oxygen (2 L/min, nasal catheter). There was subsequent clinical improvement. However, two days later, the patient died suddenly, and the circumstances of her death were consistent with the occurrence of another PE. The autopsy revealed DVT/PE without DAH or myocardial infarction.

The most important message of this report is that pulmonologists should be alert to the possibility of VTE in ANCA-associated vasculitis. Early clinical suspicion of VTE will avoid delays in diagnosis and treatment, thereby promoting better clinical results. Classically, when hemoptysis does occur (in ANCA-associated vasculitis), "it is usually related to nodules or localized infiltrates, rather than DAH", which does not include PE as a cause of hemoptysis in ANCA-associated vasculitis.[7] In addition, albeit rare, one imitator of DAH in patients with vasculitis or rheumatic disease is macrophage activation syndrome.[10]

To date, there have been only four studies specifically describing the prevalence or incidence of VTE in ANCA-associated vasculitis, and none of those studies were published in journals dedicated to pulmonology (Table 1).

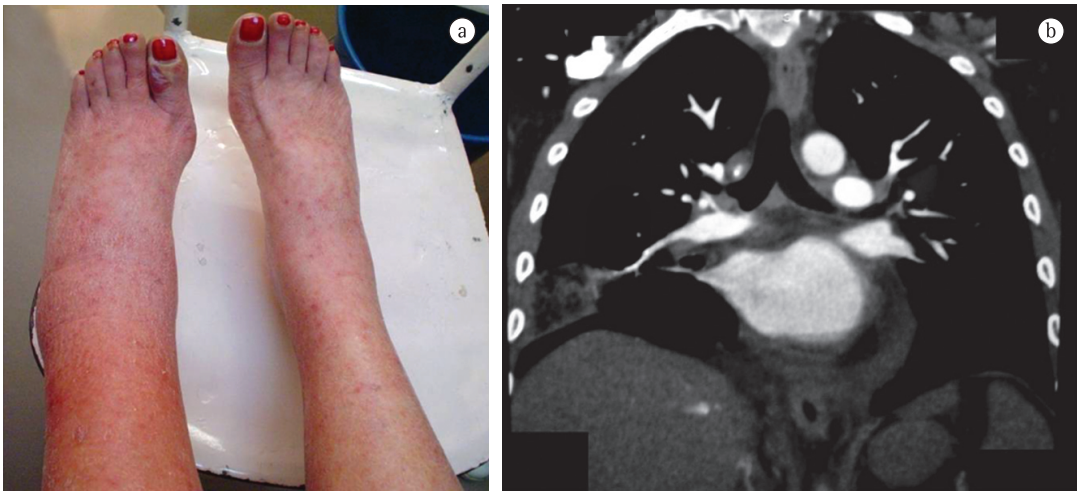

Figure 1 - In a), a photograph showing left-leg edema and palpable purpura on both legs. In b), CT pulmonary angiography showing pulmonary embolism (arrow) and pleural-based wedge-shaped-like pulmonary consolidation (consistent with pulmonary embolism-related pulmonary infarction).

[3-6] Collectively, the four studies evaluated 1,315 patients followed for 5,626.2 patient-years, VTE occurring during active ANCA-associated vasculitis in 71.5% of the cases, the incidence of VTE being 3.73/100 patient-years, and the incidence of VTE during active ANCA-associated vasculitis being 6.98/100 patient-years, which is almost as high as that observed in patients with previous idiopathic VTE (7.2/100 patient-years). The authors attribute the high rates of VTE prevalence/incidence in ANCA-associated vasculitis to the physiologic alterations induced by the vasculitis itself.[3-6] One such alteration is endothelial dysfunction, which is classically associated with ANCA-associated vasculitis and is an important component of various thrombosis/embolism-associated diseases.[1-6] In addition, the incidence of VTE is higher in the active phase of ANCA-associated vasculitis, when endothelial dysfunction/injury is more severe.[1-6] Furthermore, the endothelial dysfunction/injury in ANCA-associated vasculitis is induced by the combination of ANCA and proteinase 3 in serum. The presence of ANCA in the serum causes premature neutrophil activation, disrupting neutrophil-endothelium interactions, thereby causing deleterious endothelial damage. The proteinase 3 produced by activated neutrophils correlates with vasculitis activity and causes apoptosis of endothelial cells. Moreover,

Table 1 - Data from the four articles specifically focusing on venous thromboembolism in populations of patients with antineutrophil cytoplasmic antibody-associated vasculitis.

Article	Patients	Follow-up	VTEa/VTE	VTEa incidence	VTE incidence	VTE-related deaths
	n	patient-years	× 100%	n/100 patient-years	n/100 patient-years	n
Merkel et al.[3]	167	228.0	81.2%	NS	7.00	0
Weidner et al.[4]	105	367.5	81.2%	NS	4.30	2
Stassen et al.[5]	198	1,388.8	52.0%	6.70	1.80	0
Allenbach et al.[6][a]	845	3,641.9	NS	7.26	1.84	0
Mean	-	-	71.46%	6.98	3.73	-
Total	1,315	5,626.2[b]	-	-	-	2[b]

VTEa: venous thromboembolism in the active phase of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; VTE: venous thromboembolism in ANCA-associated vasculitis during the follow-up period as a whole; and NS: (data) not shown (in the respective original study). [a]Only data regarding ANCA-associated vasculitis were included, excluding data related to polyarteritis nodosa. [b]Estimated VTE-related mortality rate = total number of VTE-related deaths/total follow-up (patient-years) = 2/5626.2 patient-years = 0.000355 patient-years = 35.5/100,000 patient-years (95% CI: 4.3-128.2/100,000 patient-years).

the elements of Virchow's triad revisited, which proposes the mechanisms responsible for DVT/PE, are vascular endothelial injury and inflammation, both of which are present in ANCA-associated vasculitis. Finally, the presence of anti-plasminogen antibodies, which delay plasminogen-to-plasmin conversion and fibrin clot dissolution, also favors the occurrence of VTE in ANCA-associated vasculitis.

As shown in Table 1, the estimated VTE-related mortality rate in ANCA-associated vasculitis (total number of VTE-related deaths in ANCA-associated vasculitis divided by the total follow-up in ANCA-associated vasculitis) was 35.5/100,000 patient-years (95% CI: 4.3-128.2/100,000 patient-years). This is similar to the rate of hyperglycemic crisis-related mortality among diabetic adults (23.8/100,000 patient-years in the United States in 2002). All these data corroborate the epidemiological/clinical importance of VTE in ANCA-associated vasculitis.

In conclusion, pulmonologists should consider the possibility of VTE in ANCA-associated vasculitis patients with hemoptysis and dyspnea, especially during active vasculitis. Timely clinical suspicion of VTE permits early diagnosis and treatment, which is associated with better clinical results.

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