Demographic and Clinical Characteristics Associated with Central Nervous System Hemorrhage in Patients with Eosinophilic Granulomatosis with Polyangiitis: A Case Report and Review of the Literature

To the Editor:

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis affecting the small- and medium-sized arteries. It is characterized by bronchial asthma often accompanied by pulmonary infiltrates, chronic sinusitis, nasal polyps, and peripheral blood eosinophilia, and occasionally followed by a multisystem vasculitic phase involving several organs. Neurological involvement occurs in 51%–86%, usually affecting the peripheral nerves. Conversely, the central nervous system (CNS) is seldom affected (< 10%). In these cases, cerebral ischemic infarction (~80%) and diffuse encephalopathy (~10%) have been by far the findings most frequently reported. Published data on EGPA with CNS hemorrhage are limited to anecdotal case reports[1–10,11–20,21,22,23,24,25,26]. We described a case of EGPA presenting with intracerebral hemorrhage (ICH) and did a comprehensive review of the literature. Ethics board approval was not required in accordance with the policy of our hospital.

A 48-year-old man was admitted because of malaise, intermittent low-grade fever, and mild weight loss in the previous 3–4 months. One month before admission he developed numbness with paranesthesia and burning pain in the distal third of his legs. Over the preceding 18 months he referred to a persistent bronchial asthma. He denied a history of traditional cardiovascular risk factors, drug abuse, and trauma. The blood test showed leukocytosis (20.070/mm^3), eosinophilia (8.110/mm^3), C-reactive protein (CRP; 49 mg/l), erythrocyte sedimentation rate (ESR; 52 mm/h), and anti-myeloperoxidase (anti-MPO) antibodies (128 U/ml). Coagulation variables and an echocardiogram were normal. An electroneurophysiological study showed a severe axonal mixed sensitive-motor polyneuropathy in the lower limbs. EGPA was diagnosed and a 3-day course of intravenous pulses of methylprednisolone (1 g/day) was initiated. On the third day, he suddenly went into a coma and presented a left-sided hemiparesis. A head computed tomography (CT) scan disclosed a large intracranial right-sided fronto-parieto-temporal hematoma with midline shift. A CT angiogram excluded vascular malformations and arterial aneurysms. Biweekly intravenous pulses of cyclophosphamide (500 mg) and oral prednisone (30 mg/day) were started. A month later he partially recovered motility, polyneuropathy completely disappeared, and the size of the hematoma was reduced, but dysarthria remained.

Comprehensive research of the literature on CNS hemorrhage in EGPA was done [MeSH: (Churg-Strauss vasculitis or syndrome) or (eosinophilic granulomatosis with polyangiitis) and (intracerebral, cerebral, intracranial, spinal, subarachnoid, brain} and (hemorrhage, bleeding, hematoma)]. Finally, 27 case reports were considered suitable for our analysis. Also, our case was added to the series. The description of the 28 cases is summarized in Table 1 and Table 2.

No differences in sex were observed. The mean age at bleeding presentation in our series (47 ± 11 yrs) was significantly lower than the mean age of the first event of ICH in the general population (65 ± 12 yrs in men, 69.5 ± 11 yrs in women)[27]. Virtually all patients had systemic low-grade inflammation characterized by increased ESR and/or CRP, leukocytosis, and hypereosinophilia. In addition, the frequency of ANCA-positivity in our series was found to be ~2-fold higher (78%) than expected in patients with general EGPA (~40%). These results support the hypothesis that CNS hemorrhage in EGPA may substantially have a vasculitic origin.

The frequency of hypertension (HTN; usually mild to moderate) in our series was 40%, similar to that reported in patients with general EGPA. Therefore, the contribution of HTN to the CNS bleeding in these patients does not seem to be fundamental from a pathophysiological point of view.

In almost all patients, the CNS hemorrhage was preceded by a well-documented diagnosis of EGPA or a history of typical symptoms, with a highly variable interval between both events. The spectrum of clinical manifestation seen in our patients was comparable to that of the largest series and there was no clinical phenotype associated to CNS bleeding.

Several reports have shown a relatively favorable 5-year survival rate (90%–97%) for patients with EGPA[28]. In our series, mortality was 15% (4 of 26 cases). Three deaths occurred within 3 months after bleeding and a fourth at 4 years following a recurrence. So, the estimated 5-year survival rate in our series was 85% in the best-case scenario. However, the first 2 deaths occurred before 1995, when the overall prognosis of the EGPA was worse than it is currently[28]. Therefore, the short-term prognosis of EGPA patients with CNS bleeding is relatively good and possibly comparable to the rest of patients.

The most important limitation derives from the small number of cases analyzed. However, to our knowledge this is the largest series of patients with EGPA affected by CNS bleeding published in the literature[14,17].

Despite CNS hemorrhage complicating EGPA being rare (< 1%), the differential diagnosis of patients with CNS bleeding and some of the following characteristics should be taken into account: (1) relatively young patients, (2) absence of an alternative cause to explain the bleeding, (3) a history of EGPA or some of its typical symptoms, (4) coincidence with constitutional symptoms and/or multisystemic involvement, especially peripheral neuropathy, (5) demonstration of blood inflammatory markers and hypereosinophilia, and (6) positivity for ANCA, especially anti-MPO specificity.

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Table 1. Description of the case reports.

Studies	Age/sex	Site of Hemorrhage	Clinic/time before Bleeding†	pANCA/ MPO	Inflamm. Markers	Eo Count, / mm^3	Coag.	Angiography/ CT Angiogram	Asthma	Neuro-pathy	Rhinitis/ sinuso-pathy	Pulm. Infiltrates	HTN	Therapy	Outcome
Maloon, *et al*[1]	39/F	Spinal, SAH	Yes/14 mos	NR	NR	NR	Normal	Not performed	Yes	No	Yes	Yes	Yes*	PRED + CYC	Death
Chang, *et al*[2]	47/F	SAH, IVH	Yes/240 mos	NR	↑ESR, ↑CRP	22,000	NR	Not performed	Yes	Yes	Yes	Yes	NR	PRED, CYC	Death
Liou, *et al*[3]	27/M	Bilateral ICH	Yes/36 mos	pANCA	↑ESR, ↑CRP	13,250	Normal	Not performed	Yes	Yes	Yes	Yes	Yes*	MP, CYC, PRED	Imp.
Nishino, *et al*[4]	59/M	ICH	—	—	—	—	—	—	—	—	—	—	No	—	—
Ojeda, *et al*[5]	48/M	ICH	Yes/108 mos	(–)	↑ESR	6000	NR	Not performed	Yes	Yes	Yes	Yes	No	PRED, CYC	Imp.I
Calvo-Romero, *et al*[6]	47/F	SAH	Yes/72 mos	MPO	↑ESR, ↑CRP	15,200	Normal	Vasculitis	Yes	Yes	Yes	No	No	PRED, CYC	Imp.
Tyvaert, *et al*[7]	47/F	SAH, bilateral ICH	Yes/NR	MPO	↑ESR, ↑CRP	5600	Normal	Vasculitis	Yes	Yes	Yes	No	No	MP + CYC, PRED	NR
Sakamoto, *et al*[8]	36/F	SAH	Yes/96 mos	(–)	↑CRP	9515	NR	Dissecting aneurysm, vasculitis	Yes	Yes	Yes	No	No	Coil embolization, PRED	Imp.
Mishira, *et al*[9]	45/M	ICH, SAH, IVH	Yes/24 mos	(–)	↑ESR	14,600	NR	Normal	Yes	Yes	Yes	No	Yes*	PRED, CYC	Imp.
Winek, *et al*[10]	55/M	ICH	Yes/6 mos	pANCA	—	↑Eo count	—	—	Yes	—	—	Yes	—	PRED	Imp.
Sheerin, *et al*[11]	37/F	SAH	No/8 mos post-SAH	MPO	↑ESR, ↑CRP	↑Eo count	Normal	Vasculitis	Yes (post)	No	Yes (post)	Yes (post)	Yes*	MP, PRED, AZA (post)	Imp.
Nam, *et al*[12]	32/M	ICH	NR	pANCA	NR	↑Eo count	—	Normal	Yes	Yes	Yes	Yes	NR	CYC, PRED, AZA	Imp.
Shimizu, *et al*[13]	60/F	SAH	Yes/108 mos	—	—	↑Eo count	—	Normal	Yes	Yes	No	No	—	—	Imp.
Mencacci, *et al*[14]	29/M	ICH	Yes/Some mos	(–)	↑CRP	6685	Normal	Normal	Yes	Yes	Yes	No	No	MP, CYC, PRED, AZA	Imp.
Sairanen, *et al*[15]	49/M	ICH	Yes/NR	MPO, low PR3	↑CRP	9800	Mutation§, minor ASD with shunting	Minor infarctions, no aneurysm or vasculitis	Yes	No	Yes	Yes	No	MP, CYC, PRED, AZA	Imp.
Halliday, *et al*[16]	43/M	ICH, IVH	Yes/At least 36 mos	(–)	NR	13,700	No anticoagulant use, normal	Normal	Yes	Yes	Yes	Yes	Yes*	MP, CYC, PRED	Imp.
Go, *et al*[17]	39/M	SAH, IVH	Yes/7 mos	MPO	↑ESR, ↑CRP	3572	NR	Intracranial vertebral artery dissection	Yes	Yes	Yes	No	No	MP, CYC, PRED	Death
Go, *et al*[17]	46/F	ICH	Yes/120 mos	MPO	↑ESR, ↑CRP	9411	NR	Normal	No	No	Yes	Yes	NR	MP, PRED, deflazacort	Imp.
Kukita, *et al*[18]	40/F	Spinal hematoma	At onset	pANCA	NR	15,000	Normal	Not performed	Yes	Yes	Yes	Yes	No	MP	Imp.
Menditto, *et al*[19]	64/F	SAH	Yes/72 mos	MPO	↑ESR, ↑CRP	1170	Normal	PICA aneurysm, vasculitis	Yes	Yes	Yes	NR	No	Coil embolization, PRED, CYC	Imp.
Murthy, *et al*[20]	58/M	ICH	Yes/NR	MPO	NR	↑Eo count	NR	Not performed	Yes	No	Yes	Yes	Yes* (170/88)	MP, CYC, PRED	Imp.
Yeo, *et al*[21]	51/F	Spinal hematoma	Yes/NR	MPO	NR	NR	NR	Not performed	Yes	Yes	NR	NR	NR	CYC	Imp.
Ito, *et al*[22]	68/M	SAH	Yes/NR	—	—	—	—	Cerebral artery dissection	—	—	—	—	—	—	Imp.
Diamanti, *et al*[23]	31/F	SAH	Yes/NR	MPO	↑ESR, ↑CRP	13,230	NR	Not performed	Yes	Yes	Yes	No	NR	MP, PRED, RTX	Imp.
Taormina, *et al*[24]	58/M	SAH	Yes/84 mos	pANCA	↑ESR, ↑CRP	5700	NR	Vasculitis, acute ischemic lesions	Yes	No	Yes	Yes	No	PRED	Imp.
Lee, *et al*[25]	48/F	SAH, cerebellar, IVH	Yes/12 mos	MPO	NR	1553	NR	No aneurysm; vertebral artery vasculitis?	No	Yes	No (otitis, mastoiditis)	No	No	MP, PRED, CYC	Death
Aly, *et al*[26]	59/M	ICH, ischemic infarcts	Yes/NR	MPO	↑ESR, ↑CRP	Normal count	NR	Not performed	Yes	Yes	No	No	Yes	PRED	Imp.
Our case	48/M	ICH	Yes/18 mos	MPO	↑ESR, ↑CRP	8110	Normal	Normal	Yes	Yes	Yes	No	Yes	MP + PRED + CYC	Imp.

† Time before bleeding: Time since the first symptom attributed to EGPA to CNS hemorrhage presentation. * Hypertension coinciding with the bleeding. § Heterozygotic clotting factor V R506Q mutation. ANCA: antineutrophil cytoplasmic antibodies; pANCA: peripheral ANCA; MPO: myeloperoxidase; Eo: eosinophils; CT: computed tomography; F: female; M: male; SAH: subarachnoid hemorrhage; IVH: intraventricular hemorrhage; ICH: intracerebral hemorrhage; NR: not reported; —: data not reported in the abstract; (–): negative; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ↑Eo count: hypereosinophilia; ASD: atrial septal defect; PICA: posterior inferior cerebellar artery; PRED: oral prednisone; CYC: cyclophosphamide; MP: methylprednisolone; AZA: azathioprine; RTX: rituximab; Inflamm.: inflammatory; Imp.: improvement; Pulm.: pulmonary; Coag.: coagualtion.

Table 2. Characteristics of EGPA patients with CNS hemorrhage. Values are n (%) unless otherwise specified.

Characteristics	Values
Age at bleeding presentation, yrs	
Mean ± SD	47 ± 11
Median (IQR)	47 (39–57)
Range, yrs	27–68
Male	15/28 (53.5)
History of EGPA or of any typical symptom of EGPA	
Pre-bleeding	24/26 (92.3)
Post-bleeding	1/26 (3.8)
During bleeding	1/26 (3.8)
Time EGPA, bleeding*, mos	
Mean ± SD	66 ± 60
Median (IQR)	72 (13–102)
Range	0–240
Site of hemorrhage†	
Subarachnoid	14/28 (50.0)
Intracerebral	13/28 (46.4)
Spinal	3/28 (10.7)
Intraventricular	5/28 (17.9)
Multiple location	8/28 (28.6)
Ischemic events coexistence	3/28 (10.7)
Clinical manifestations†	
Asthma	24/26 (92.3)
Rhinitis/sinusopathy	21/24 (87.5)
Neuropathy	19/25 (76.0)
Pulmonary infiltrates	13/24 (54.2)
Hypertension	8/20 (40.0)
Inflammatory markers	17/17 (100)
Eosinophilia	23/24 (95.8)
ANCA	
pANCA and/or MPO specificity	18/23 (78.3)
Angiography/computerized tomography angiogram	
Normal	7/17 (41.2)
Vasculitis	8/17 (47.1)
Aneurysm/dissection	4/17 (23.5)
Death	4/26 (15.4)
Poor evolution during the hospitalization	2/4
Recurrence of bleeding 4 years after first event	1/4
Recurrence complicated with infective ventriculitis	1/4

* Elapsed time between onset of EGPA (diagnosis or first typical manifestation) and the hemorrhage occurrence. † Cumulated frequencies. EGPA: eosinophilic granulomatosis with polyangiitis; CNS: central nervous system; IQR: interquartile range; ANCA: antineutrophil cytoplasmic antibodies; pANCA: peripheral ANCA; MPO: myeloperoxidase.

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