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Original Article

Outcome of Localized Granulomatosis with Polyangiitis: A Case Study

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Objective. A substantial portion of granulomatosis with polyangiitis (GPA) patients present with localized disease limited to the upper respiratory tract, however; disease spectrum and prognosis of these patients are unclear. The aim of this study is to describe the clinical characteristics and outcome of patients with localized GPA. **Methods.** This was a retrospective descriptive case series of patients with a biopsy proven localized GPA presenting to a single tertiary rheumatology service between January 1995 and September 2015. **Results.** A total of 5 patients, median age 56 years (range 48 to 59 years) at diagnosis and 80% female, were identified. The median follow-up period was 42 months (range 15 to 62 months). Diagnosis was delayed with median time to diagnosis of 12 months (range 3 to 36 months), and patients underwent 1-3 ear, nose, and throat surgeries during the period of diagnostic delay. Sinusitis was the most frequent symptom in all patients, followed by otomastoiditis with cranial nerve palsies (n = 2) and orbital mass (n = 1). Antineutrophil cytoplasmic antibody (ANCA) was positive initially in 2/5 patients (40%). Two patients with otomastoiditis and cranial nerve palsies progressed to systemic disease with ANCA positive conversion. These two cases along with a case with orbital mass were refractory to standard treatment of cyclophosphamide with glucocorticoids requiring rituximab treatment. **Conclusion.** Patients with localized GPA may progress to systemic disease over the disease course, and may have aggressive disease refractory to standard treatment. Close monitoring for systemic symptoms and repeated ANCA testing is required in patients with localized GPA. **(J Rheum Dis 2016;23:174-178)**

Key Words. Granulomatosis with polyangiitis, Localized, Outcome

INTRODUCTION

Granulomatosis with polyangiitis (GPA) is a necrotizing granulomatous vasculitis with multi-systemic involvement. Two forms of GPA have been described; the classical systemic form involving upper and lower respiratory tract and kidney and localized form limited to mostly upper respiratory tract. In few studies, localized GPA has been described to have more granulomatous lesions on biopsy, less antineutrophil cytoplasmic antibody (ANCA) positivity, and milder disease course [1-3]. However, there are limited data available on disease spectrum and long term prognosis of patients with localized GPA to determine whether localized GPA is a distinct phenotype or a manifestation of early stage of GPA which may progress into systemic type. We present here a retrospective series of 5 patients with biopsy proven localized GPA. The aim of this study is to describe the clinical characteristics and outcome of patients with localized GPA.

MATERIALS AND METHODS

We conducted a retrospective analysis including patients diagnosed or suspected of GPA at Ewha Womans University Mokdong Hospital between January 1995 to September 2015. For this case study, only patients who had localized disease limited to upper and/or lower respiratory tract by European Vasculitis Study (EUVAS) defi-

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nition [4], and biopsy findings compatible with GPA were selected. Patients with orbital mass were considered as localized disease although orbit is not a part of the respiratory tract [4]. Disease stages of localized, early systemic, and generalized were defined according to EUVAS definition [4]. We reviewed the medical records of the selected patients and collected the clinical, laboratory and histologic data. This study was approved by the regional Institutional Review Boards of Ewha Womans University Mokdong Hospital (IRB no. 2016-03-029).

RESULTS

Clinical and histologic characteristics

Five patients fulfilled the inclusion criteria of whom 4 (80%) were women. The median age was 56 years (range 48 to 59 years). The interval from first symptom to diagnosis was median 12 months (range 3 to 36 months). Initial clinical and histologic characteristics were summarized in Table 1. All patients had ear, nose, and throat (ENT) manifestations as initial symptoms and 4 patients (80%) received 1-3 surgeries related to ENT manifestations before the diagnosis of GPA. Sinusitis was present in all patients. Manifestations other than sinusitis were otomastoiditis with cranial nerve palsies (n=2) and orbital mass (n=1) (Figure 1). Case 1 presented bilateral facial nerve palsies, and Case 3 had multiple debilitating lower cranial nerve palsies from VII to XII in association with otomastoiditis. In cases with symptoms other than sinusitis showed local bone destruction on imaging.

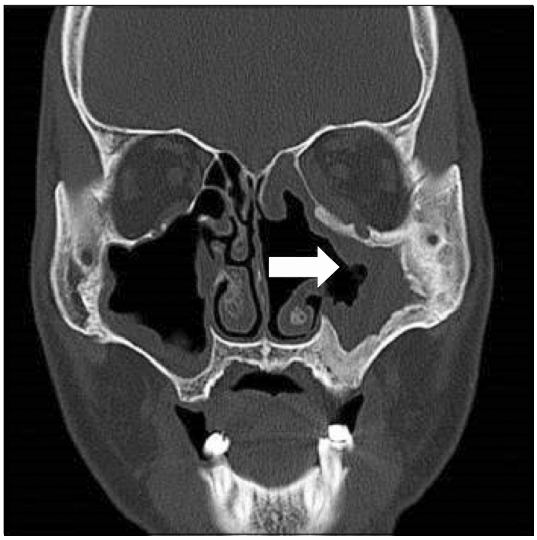

Figure 1. Case 1 in 2012. Computed tomography of paranasal sinus image showed mass extends to the intraorbital portin of the left oribt (arrow). Soft tiss densities along the both maxillary and frontoethmoidal sinuses.

Table 1. Initial clinical and histologic characteristics of patients with localized GPA

Variable	Case				
	1	2	3	4	5
Sex	Female	Male	Female	Female	Female
Age at diagnosis (yr)	48	56	58	59	56
Time to diagnosis (mo)	9	36	15	3	12
Initial symptoms	Sinusitis, otitis, mastoiditis, and bilateral facial nerve palsy	Sinusitis, and orbital mass	Sinusitis, otitis, mastoiditis, and multiple lower cranial nerve palsies	Sinusitis	Sinusitis
Number (type) of surgery performed	1 (Bilateral mastoidectomy)	3 (FESS, uncinectomy, ethmoidectomy)	1 (FESS)	0	1 (Infundibulectomy)
Histologic features	Granuloma, necrosis, vasculitis*	Granuloma, necrosis, vasculitis	Granuloma, necrosis, vasculitis	Granuloma	Granuloma, microabscess
Local bone destruction	Nasal bone, septum, and sphenoid bone	Intraorbital portion of the left orbit wall	Bilateral orbit	No	No
ANCA positivity	Negative	PR-3	Negative	MPO	Negative

ANCA: antineutrophil cytoplasmic antibody, FESS: functional endoscopic sinus surgery, GPA: granulomatosis with polyangiitis, MPO: myeloperoxidase, PR-3: proteinase-3. *Initially negative but GPA proven by biopsy after developing early systemic/generalized disease.

All patients underwent at least one biopsy procedure. Granuloma was a common feature found in all patients, followed by necrosis (n=3), vasculitis (n=3), and microabscess (n=1). ANCA was positive initially in 2/5 (40%) of the cases.

Outcome and treatment of the patients

The patients were followed up for median duration of 42 months (range 15 to 62 months). Clinical outcome and treatment of the patients were summarized in Table 2. During the follow up, 2 patients (40%; Case 1, Case 3) progressed into systemic disease. ANCA was initially negative but became positive as these patients developed systemic disease. Of note, diagnosis of GPA could not be made in Case 1 since repeated biopsies revealed nonspecific inflammation. However, 9 months after initiation of ENT symptoms, the patient developed acute nasal swelling accompanied by fever, weight loss, and multiple cervical lymphadenopathies, and myeloperoxidase (MPO) ANCA became positive. At this time, the diagnosis of GPA was confirmed histologically (Figure 2). Case 3 developed polydipsia and polyuria during follow up 36 months after the diagnosis of localized GPA. Clinical and laboratory findings were compatible with central diabetes insipidus, and brain magnetic resonance imaging revealed enhancing 10.5 mm pituitary mass and thickened stalk suggestive of pituitary gland involvement of GPA (Figure 3). Similarly with Case 1, proteinase-3 (PR-3)

Table 2. Outcome and treatment of patients with localized granulomatosis with polyangiitis

Variable	Case				
	1	2	3	4	5
Median follow up duration (mo)	32	42	48	62	15
Development of systemic disease	Yes	No	Yes	No	No
Time to diagnosis* (mo)	Diagnosis made at onset of systemic disease	NA	36	NA	NA
Symptoms †	Fever, weight loss, lymphadenopathy, and acute nasal swelling	NA	Pituitary gland involvement (diabetes insipidus)	NA	NA
ANCA positivity ‡	Yes (MPO)	NA	Yes (PR-3)	NA	NA
Refractory disease	Yes	Yes	Yes	No	No
Treatment	CS, CY, MTX, RTX	CS, CY, RTX	CS, CY, RTX	CS, CY, MTX	CS, MTX
Current status of follow up	Out-patient	Out-patient	Out-patient	Out-patient	Out-patient

ANCA: antineutrophil cytoplasmic antibody, CS: corticosteroid, CY: cyclophosphamide, MPO: myeloperoxidase, MTX: methotrexate, NA: not applicable, PR-3: proteinase-3, RTX: rituximab. *Time from diagnosis to systemic disease. †At development of systemic disease. ‡Conversion to ANCA positivity at development of systemic disease.

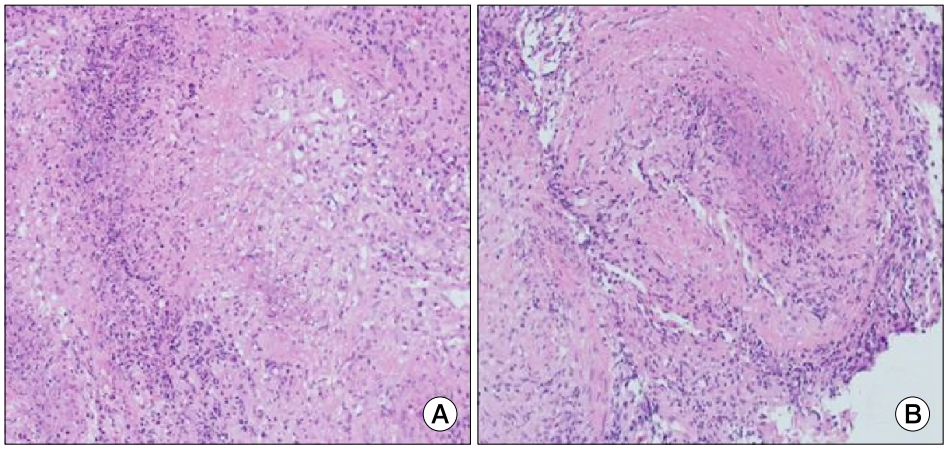

Figure 2. Case 1 in 2013. Nasopharyngeal biopsy revealing granulomatous inflammation with palisading necrosis (A), and vasculitis (B) (H&E, ×200).

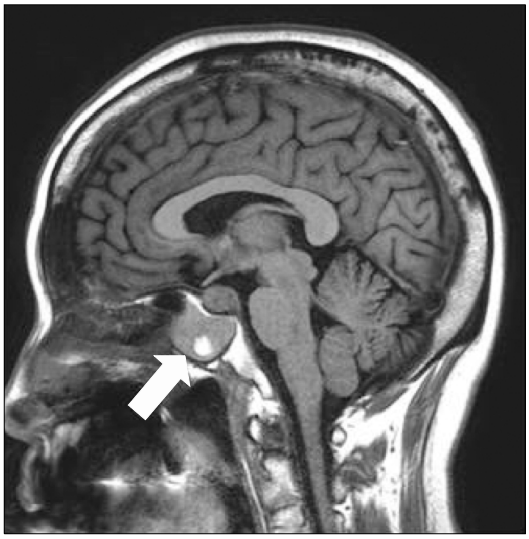

Figure 3. Case 3 in 2014. Gadolinium enhanced T1-weighted sagittal magnetic resonance image showed diffuse enlargement of pituitary gland (11.5 mm in height) with thickened enhanced pituitary stalk (arrow).

ANCA became positive as pituitary gland involvement developed.

Three cases (60%) were refractory to standard treatment of cyclophosphamide with glucocorticoids requiring rituximab treatment. Refractory cases were Case 1 and Case 2 who developed systemic disease and Case 3 with orbital mass. In these refractory cases, rituximab was effective in controlling systemic disease activity but ineffective in resolving the mass lesion. Orbital mass in Case 2 and pituitary mass in Case 3 persisted despite rituximab treatment. Death did not occur in any of the cases and all cases are currently under follow up in the out-patient clinic.

DISCUSSION

In this case study, we observed that patients with localized GPA may have aggressive disease refractory to standard treatment, and may progress into systemic disease over the disease course. Patients with aggressive form of localized GPA had clinical symptoms of locally invasive destructive inflammation along anatomical pathway of ENT such as orbital mass and cranial nerve palsies.

Localized form of GPA was described in several previous studies as a distinct subtype of GPA with milder disease opposed to classic GPA with fulminant life threatening disease [5-9]. However, Boudes [10] first proposed in 1990 that localized GPA is a part of the multistep disease process of initial pure granulomatous phase, subsequent localized stage, and ultimate generalized vasculitis with renal involvement. Boudes [10] proposed this concept based on the pathogenetic mechanism of initial granulomatous inflammation proceeding to systemic vasculitis. For purposes of conducting in clinical trials, EUVAS and the Wegener's Granulomatosis Etanercept Trial (WGET) groups incorporated the concept proposed by Boudes [10] and classified GPA patients into 4 disease states: localized, early systemic, generalized, and severe renal disease [4]. However, whether these disease states were part of a multistep disease process or a distinct subset was vastly unknown due to lack of prospective long term follow up studies. In a recently published prospective long term follow up study, it was reported that 5% of the patients with localized GPA progressed into systemic disease. We found that 40% of the cases progressed into systemic disease suggesting that progression into systemic disease is not an infrequent event and may represent early form of systemic GPA.

Diagnosis of localized GPA is often a challenge since most of the patients present with manifestations of common ENT disease such as sinusitis and otitis media. High clinical suspicion and biopsy confirmation in atypical cases were reported to be important in leading to correct diagnosis [11]. ANCA positivity was reported to be highly specific the diagnosis of GPA [12], but approximately half of the patients with localized GPA were reported to be ANCA-negative making the diagnosis more difficult [3]. In addition, only 35.7% of the patients with localized GPA were observed to have pathologic features characteristic of GPA [13]. Diagnostic histopathological features of GPA are granuloma and vasculitis. In cases of localized GPA, granuloma was suggested as a predominant feature, and vasculitis and granuloma at the same time were observed in only 21% to 32% of the biopsies [3,14]. In our case series, we also encountered diagnostic difficulties. We observed that diagnosis was delayed by median 12 months, and patients received multiple unnecessary surgical procedures before the diagnosis of GPA for refractory sinusitis and otomastoiditis. Initial ANCA testing was positive in only 40% of the cases. In one case, pathologic confirmation was obtained only after the development of systemic symptoms since repeated biopsies from ENT tract revealed non-specific inflammation.

Localized GPA shows relatively mild disease course, but may undergo an aggressive course refractory to conventional treatment of cyclophosphamide with glucocorti-

coids in some proportion of patients. Holle et al. [3] reported in prospective follow up of 50 patients with localized GPA that although 34% achieved complete remission, 46% of the patients relapsed, and 10% progressed into systemic disease. Relapse rate was compatible with that of generalized disease [1]. Patients with orbital masses were reported to be associated with the highest rate of refractory disease [3]. Similarly, we found that 3 of 5 patients (60%) showed aggressive course refractory to standard treatment. Of note, 2 of these patients had initial clinical manifestations of cranial nerve palsies in addition to ENT manifestations, and progressed into systemic disease with ANCA positive conversion at the time of systemic disease development. One patient had orbital mass. Pathologically, these 3 patients had both granuloma and vasculitis features on biopsies. Rituximab was reported to be less effective in granulomatous component of the disease than in the vasculitic component of the disease [15], thus aggressive form of the localized GPA, especially in cases with formation of masses, early diagnosis of localized GPA at the onset of the disease process would be clinically important. We also observed that rituximab was not effective in reducing masses in 2 cases with refractory disease.

The limitation of our study is that this is a case study of rare disease including small number of patients. Large cohort of patients is required to further define the prognosis of patients with localized GPA.

CONCLUSION

Patients with localized GPA can progress into systemic disease, and may undergo aggressive disease course refractory to standard treatment. Close monitoring for systemic symptoms and repeated ANCA testing is required in patients with localized GPA, especially in patients with locally invasive disease.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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