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Granulomatosis with polyangiitis in Tunisia

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SUMMARY

Granulomatosis with polyangiitis (GPA) is more frequent in Northern rather than Southern countries. Very few studies have been conducted in Africa. We have performed a retrospective descriptive study including clinical and laboratory profiles of 30 Tunisian GPA patients seen at the department of Internal Medicine of the University Hospital of la Rabta from 2000 to 2014. Mean age at initial GPA diagnosis was 46±12 years, and the average number of months between the onset of symptoms and diagnosis was 25. Seventeen (56%) were male, and 13 (44%) were female. Ear/nose/throat involvement occurred in 83%. Lung and renal involvement were observed in respectively 70% and 56% followed by mucocutaneous (50%), neurological (50%), ocular (33%), vascular (20%), ureteral (16%), and cardiac involvement in 10%. Cytoplasmic pattern-antineutrophil cytoplasmic antibodies (ANCA) was detected in 27 (90%) patients. Induction therapy consisted of intravenous cyclophosphamide pulses in 27 patients (90%) and oral methotrexate in 3 patients (10%). Trimethoprime-sulfamethoxazole was used in 26 patients (86%). Maintenance therapy consisted of azathioprine in 17 cases and methotrexate in 13 cases. Relapses occurred in 36%. Eighteen patients had favorable outcome and 12 died. Our patients had a distinct phenotype with high prevalence of pleural involvement, lymph node enlargement, sensorimotor neuropathy and ureter stenosis. ENT symptoms were less frequent as inaugural presentation. Overall 2-year survival was 60%.

Key words: *Vasculitis; epidemiology.*

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INTRODUCTION

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis or disease was first described in 1931 by Klinger, with the clinical and pathological unique features added to the description in 1936 by Wegener (1). This clinicopathological disease is characterized by granulomatous necrotizing inflammatory lesions of the upper and/or lower respiratory tract, associated to pauci-immune glomerulonephritis, and small-vessel vasculitis (2). Descriptive epidemiological studies have suggested that GPA is more common in the north of Europe than in the south or in Asia (3). There are very limited data in the literature concerning GPA in Africa (4).

Due to insufficient clinical data concerning GPA in Maghreb, we have conducted a retrospective, descriptive study of Tunisian GPA patients.

PATIENTS AND METHODS

The present work is a single center retrospective study of 30 patients with GPA who were diagnosed between January 2000 and January 2014 and were followed up at the Department of Internal Medicine of the University Hospital of la Rabta in Tunis. All of the patients who were included in the present study met at least 2 of the 5 modified classification criteria of the American College of Rheumatology (5). The definitions of organ damage were based on clinical and laboratory criteria according to the EULAR Recommendations for Conducting Clinical Studies and/or Clinical Trials in Systemic Vasculitis (6). Information on clinical manifestations, laboratory findings, histopathology, radiology, disease course, and treatment was obtained through interview and by reviewing the medical records. A standard form was used to collect clinical findings related to

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Table I - Clinical features in 30 granulomatosis with polyangiitis Tunisian patients.

	Inaugural GPA symptoms	GPA symptoms at follow-up
Organ involvement	**No. patients (percentage)**	**No. patients (percentage)**
Constitutional symptoms		18 (60%)
ENT involvement	17 (56%)	25 (83%)
Crusting rhinitis		10 (33%)
Epistaxis		8 (26%)
Pansinusitis		9 (30%)
Otitis media		5 (16%)
Hearing loss		4 (13%)
Pulmonary involvement	9 (30%)	21 (70%)
Hemoptysis		11 (36%)
Dyspnea		9 (30%)
Pulmonary nodules/cavities		13 (43%)
Interstitial lung disease		9 (30%)
Pleural effusion		5 (16%)
Alveolar condensation		5 (16%)
Renal involvement	4 (13%)	17 (56%)
Proteinuria		17 (56%)
Hematuria		15 (50%)
RPGN		13 (43%)
Neurological involvement		15 (50%)
Peripheral neuropathy		11 (36%)
Cranial palsies		4 (13%)
Pachymeningitis		2 (6%)
Cerebral venous thrombosis		1 (3%)
Mucocutaneous involvement		15 (50%)
Vascular purpura		9 (30%)
Gingivitis		4 (13%)
Subcutaneous nodules		3 (10%)
Oral ulceration		2 (6%)
Digital gangrene		2 (6%)
Cardiac involvement		3 (10%)
Mitral insufficiency		2 (6%)
Pericarditis		2 (6%)
Myocarditis		1 (3%)
Ophthalmological involvement		10 (33%)
Exophthalmos		3 (10%)
Conjunctivitis		3 (10%)
Ureteral stenosis		5 (16%)
Retroperitoneal fibrosis		3 (10%)
DVT/PE		6 (20%)
Arthritis		7 (23%)

GPA, granulomatosis with polyangiitis; ENT, ear/nose/throat; RPGN, rapidly progressive glomerulonephritis; DVT, deep venous thrombosis; PE, pulmonary embolism.

GPA. Statistical analysis was conducted using the SPSS statistical package (version 18). Continuous variables are expressed as the mean and SD. Number (n) and percentages were calculated for categorical variables. Mean and proportions 95% confidence intervals (CI) were calculated.

RESULTS

Thirty GPA patients were evaluated, 17 (56%) were male, and 13 (44%) were female. The mean age at diagnosis was 46±12 years. The average time between the onset of symptoms and diagnosis was 25 months. Inaugural manifestations were predominantly ENT and lung symptoms in 56% and 30% each (Table I). Eighteen patients (60%) had constitutional symptoms such as prolonged fever, fatigue or weight loss. Ear, nose and throat (ENT) involvement was present in 25 patients (83%). Crusting rhinitis was the most frequent symptom present in 10 patients (33%). CT sinus scan, performed in 13 cases, showed destructive pansinusitis in 9 cases, middle nasal concha lysis in 3 cases, and nasal septum deviation in 2 cases. ENT biopsy was performed in 11 patients: nasal mucosal in 4, sinus and nasopharyngeal in 3 cases each and palate in 1 case. The pathological findings were of GPA in 7 cases, unspecified inflammation in 2 cases, and were normal in 2 cases. Pulmonary involvement was present in 21 patients (70%). Hemoptysis (36%) and shortness of breath (30%) were highly prevalent. Three patients had pulmonary involvement at checkup while they were totally asymptomatic. Seventeen patients underwent bronchoalveolar lavage and were negative for any type of germ. Lungs CT scan showed nodules and cavities in 13 cases (43%), alveolar condensation in 5 cases (16%), alveolar hemorrhage in 3 cases (10%), interstitial lung disease in 9 cases (30%), pleural effusion in 5 cases (16%), and mediastinal lymph node enlargement in 9 cases (30%). Bronchial biopsy was performed in 4 patients and showed granulomatous inflammation in 2 cases. Surgical biopsy of lungs was performed in 2 patients and revealed necro-

tizing vasculitis. In addition, renal involvement was observed in 17 patients (56%). Proteinuria (median: 1.4 g/24 hours, extremes 0.3 g to 5 g/24 hours) was observed in 17 patients (56%), hematuria in 15 cases (50%) (microscopic hematuria in 10 cases and macroscopic in 5 cases), and rapidly progressive glomerulonephritis in 13 cases (43%).

Thirteen kidney biopsies were performed. According to the pathological classification of ANCA-associated vasculitis glomerulonephritis outlined by Berden et al. (7), 8 biopsies were classified as crescentic, 4 as focal, and 1 biopsy as sclerotic. Tubulointerstitial lesions were observed in 1 case. Renal involvement was significantly associated with poor prognosis (p=0.014).

Neurological involvement was observed in 15 patients (50%). Peripheral nervous system involvement occurred in 11 cases (36%), represented by sensorimotor polyneuropathy in 9 cases, mononeuritis multiplex in 2 cases, and cranial palsies in 3 cases. Optic neuritis was observed in 2 patients, concomitant olfactory and oculomotor nerves involvement, facial palsy and vestibular nerve involvement in one case each. Central nervous system involvement was observed in 3 cases (10%). Cerebral MRI revealed cerebral venous thrombosis in 1 case, and pachymeningitis in 2 cases. Neurological involvement was significantly associated with the positivity of ANCA antibodies (p=0.03).

Mucocutaneous manifestations, which occurred in 15 cases (50%), were purpura (30%), localized and hypertrophic gingivitis (13%), subcutaneous nodules (10%), oral ulceration (6%), and digital gangrene (6%). We reported an association with a pyoderma gangrenosum in one patient. Mucocutaneous involvement was significantly associated with favorable outcome (p=0.01). Cardiac manifestations were reported in 3 patients (10%): mitral insufficiency, pericarditis in 2 cases each, and myocarditis in 1 case. Cardiac involvement was significantly associated with favorable outcome (p=0.01). Ophthalmologic involvement was observed in 10 patients (33%). Exophthalmos and conjunctivitis were the most frequent signs in 3 patients each. Episcleritis was reported in 1 case. Orbital MRI revealed intra orbital pseudo tumor in 2 cases and hypertrophic lacrimal gland in 1 case.

Ureteral stenosis was observed in 5 patients. Retroperitoneal fibrosis was objectified in 3 cases. Six patients (20%) developed deep venous thrombosis/pulmonary embolism during the study period. Articular involvement, with non-deforming arthritis involving medium-and large size joints, occurred in 7 patients (23%).

The signs and symptoms of GPA that were present at disease onset and during the course of illness are summarized in Table I. The presence of ANCA was determined by immunofluorescence testing in all of the patients.

Twenty-seven patients were ANCA positive (90%); 24 patients (80%) showed a cytoplasmic staining pattern (c-ANCA), whereas 3 patients (10%) had a perinuclear pattern (p-ANCA). An enzyme-linked immunosorbent assay (ELISA) test was available in only 21 patients in our series; 17 patients were c-ANCA/PR3 positive, and 4 patients were p-ANCA/MPO positive. Induction therapy consisted of intravenous cyclophosphamide pulses in 27 patients (90%) and oral methotrexate in 3 patients (10%).

Trimethoprime-sulfamethoxazole was used in 26 patients (86%). All patients had oral prednisone, starting with 1 mg/kg/day, and maintained for at least 2 months before gradual reduction during the following 10 months. Maintenance therapy consisted of azathioprine in 17 cases and methotrexate in 13 cases.

The mean period of observation was 25 months. Over the follow up period, 11 patients (36%) relapsed. ANCA antibodies were positive in 8 of the 11 patients who relapsed. Eighteen patients had favorable outcome and 12 patients died within 2 years of disease onset. Overall 2-year survival was 60%. Six patients died due to septic shock, 2 died as a consequence of neoplasm (schwannomma and lung cancer), 2 died as a consequence of alveolar hemorrhage, and 2 due to pulmonary embolism.

DISCUSSION

GPA is a systemic, necrotizing, granulomatous, ANCA-associated small-vessel vasculitis, primarily involving the respiratory tract and the kidneys. The reported incidence of GPA varies from 2 to 12 per million people and the prevalence is from 24 to 157 per million people. Different studies have demonstrated geographical variation along a north-south axis in the northern hemisphere (3). Ethnicity may also be relevant because GPA is rarely seen in Africa. Only a few African studies have addressed vasculitis. In a retrospective study of 27 cases of systemic vasculitis in Senegal, GPA was diagnosed in 2 cases (4). To the best of our knowledge, this is the first North African study that describes the demographic and the clinical manifestations and the treatment outcomes of Tunisian GPA patients, and compares this cohort to other previously described ones. The mean age at diagnosis was 46 years old. This is in alignment with literature data that highlight a peak incidence in the fourth through sixth decades of life; by contrast, it is very much less common in children. Commonly, there is no gender predominance in GPA and the sex ratio in our series (M/F) was 1.4 (8). In our series, ENT involvement was high, but inaugural in only 56% of cases, which is less frequent than in previously reported series. ENT symptoms are often insidious and thus misdiagnosed (9, 10). In our case series, patients with ENT manifestations were first checked by physicians who are not aware of this disease, as the manifestations are unspecified and because of other more frequent conditions such as infections and allergies. Their recognition is important in order to make the diagnosis and prevents advanced disease with scarred areas in the nasal mucosa or erosion of the turbinates and septum. Moreover, the ENT sphere has good accessibility for the biopsy of the nasal fossae and/or sinus. It requires a good technique, with multiple specimens in the granulomatous area rather than in the necrotic area. Despite its simplicity, sensitivity is lower than with lung biopsy. In our cases series, ENT biopsies were contributive in 63% of cases. Therefore, it is important for ENT specialists to become familiar with these diseases (11, 12). This series illustrates many of the pulmonary manifestations associated with this disease described in the literature. The prevalence of pulmonary involvement corresponding with those reported in the literature was 70% (respectively 70 and 73%) (13, 14). Pulmonary nodules accompanied by cavities were the main imaging finding (43% of cases) corresponding with those reported in the literature (15).

Moreover, interstitial lung disease resulting from alveolar hemorrhage, alveolar condensation representing pulmonary infarction, and pleural effusion were the most frequent manifestations reported in our series (respectively 30%, and 16% each). The particularity of this series is the high prevalence of pleural involvement and mediastinal lymph node enlargement in comparison with previous reported cohorts (respectively 5% and 15%) (14, 15). Alveolar hemorrhage, often caused by ANCA-mediated vasculitis, was present only in 3 patients (10%), which is much lower than in the French series (16). The other particularity of our series is the diagnostic difficulties in a country with a high prevalence of tuberculosis that must be considered at time of diagnosis and after administration of immunosuppressive agents. In our series, patients with lung involvement underwent standard bacteriological investigations to rule TB out systematically but also other infectious complications (fungi and mycobacteria). Clinical or morphological evidence of renal involvement has been found in about 80% of patients with GPA. Prevalence of ANCA vasculitis in our study was lower than that reported. This discrepancy relates to the fact that patients with severe renal involvement were oriented to a nephrology unit. In our series, renal involvement was inaugural in 13% of cases and its prevalence during the study period was 56%. The review of the literature shows that inaugural renal involvement will be around 18% and its prevalence will increase during the course of the disease course to achieve a median

of 70% (38-100%) (17, 18). Rapidly progressive glomerulonephritis also named necrotizing crescentic glomerulonephritis or pauci-immune glomerulonephritis is the third main manifestation of GPA, noted in 40 to 100% of patients depending on the series. Proteinuria is often less than 3g/24 hours but could be nephrotic in 10 to 40% of cases (18, 19). Renal biopsies were performed in 13 patients and showed classically pauci-immune crescentic glomerulonephritis as found in the majority of GPA patients. Moreover, the tubulointerstitial lesions in GPA were largely correlated to worse renal outcome (20). Renal involvement in our patients was significantly associated with poor prognosis, in accordance with previous studies (19, 21). Ureteral stenosis was reported in 5 cases (16%) in our series. The review of literature reported 17 cases. Pelvic ureter was predominantly involved and that could be unilateral or bilateral. This feature is usually revealed by urinary infection, hematuria or obstructive renal insufficiency, associated with retroperitoneal fibrosis in 3 cases. That is to say, ureteral stenosis in GPA is probably underestimated and physicians should be aware of these unusual presentations (22). Ureteral stenosis can be due to small vessel vasculitis or secondary to extrinsic compression due to retroperitoneal fibrosis. In our case series, ureteral involvement related to GPA was retained after ruling out classical causes such as ureteral neoplasm, chronic infection sequelae, or urogenital tuberculosis. The high rate of ureteral stenosis in our case series is due to Peripheral nervous system involvement which occurs in one third of patients, mainly represented by mononeuritis multiplex (79% of the patients with peripheral neuropathy), then sensorimotor polyneuropathy. Contrary to published data, in our series, sensorimotor polyneuropathy was more frequent than mononeuritis multiplex (respectively 30% and 6%) (23, 24). Central nervous system (CNS) involvement is less common and can be observed in 6 to 13% of patients (10% in our series), usually later in the course of the disease. Initial presentation with pachymeningitis is one of the CNS manifestations described, which is suggestive, but not specific, for GPA (25). Mucocutaneous involvement occurred in 50% of patients, with palpable vascular purpura and hypertrophic gingivitis (strawberry-like gum) as the most frequent manifestations (respectively 30% and 13%). Subcutaneous nodules, or cutaneous ulcerations/gangrene are less frequent but suggestive of the disease (26). Pyoderma gangrenosum was reported in one case. This could be a fortuitous association. Cardiac manifestations are reported with a frequency varying from 0 to 12% (27). In our series, 3 patients (10%) had cardiac involvement. Although histological proof is lacking, the temporal relation of the condition to active GPA is striking. These rare manifestations were attributed to GPA because they were diagnosed during disease course and responded to specific treatment. The ocular manifestations range from mild conjunctivitis and episcleritis to more severe inflammations with keratitis, scleritis, uveitis, and retinal vasculitis. In our series, conjunctivitis and exophthalmos were the most frequent.

Exophthalmos was the consequence of orbital granuloma or pseudo-tumor that may compress muscle or nerve and worsen the visual prognosis. Its management is challenging and often requires a multidisciplinary approach (28). Deep venous thrombosis and pulmonary embolism occurred in 6 patients (20%) which highlights the higher risk of venous thrombosis in GPA patients, especially during the active phases of the disease. In fact, the incidence rate of venous thrombosis was 7 per 100 patients/year, as compared with 0.3 per 100 patients-year in the general population; this finding would justify closer monitoring of the patients for those events, but could not be used to justify systematic prophylaxis with anticoagulation for all patients (29). Articular involvement, which occurred in 23% of our patients, seems to be less frequent than literature data. In fact, non-deforming polyarthritis involving medium- and large-size joints is reported in two thirds of the patients (8). The immunological findings were very suggestive of the diagnosis in the majority of patients reveal-

ing anti-PR3 ANCA and anti-MPO ANCA, usually described in GPA. The Combination of both indirect immunofluorescence (IIF) and ELISA improves the specificity of the tests for GPA. The diagnosis sensibility increased to 73% with a specificity of 99%when results of the IIF test (c-ANCA or p-ANCA) were used together with the results of PR3 and MPO (30). The combination of steroids and cyclophosphamide at induction phase (90% of patients) followed by azathioprine or methotrexate (56% and 44% respectively) was the most used therapeutic regimen and associated with the remission rate of 48% in our patients.

The cyclophosphamide pulses are as efficient as the oral route and well tolerated. Methotrexate is equivalent to azathioprine for the maintenance period. Its prescription should be restricted to patients with localized forms of GPA and during maintenance period (31, 32). Interestingly, recent randomized controlled trials with rituximab have shown a similar efficacy to CYC in the induction of remission with reduced adverse effects. In the present series, rituximab was not used (33). Over the follow up period, 16 patients developed serious infectious complications, 2 oncologic complications, and 3 diabetes. The concomitant use of cotrimoxazole may explain the fact that we did not observe a single case of P. jiroveci pneumonia, in contrast to several reports that emphasized a high P. jiroveci pneumonia incidence in GPA patients. There were no cases of tuberculosis, even though it is a very prevalent disease in our country (34). In this study and during study period, we did not record any arterial thromboembolic events, contrasting with the reported series. Conversely, we found a high prevalence of venous thrombosis (35). GPA is a potential relapsing disease. The relapse rate, however, varies between series from 10 to 50% and was 36% in our patients (36).

The overall 2-year survival was 60%, which confirmed the previous data (37). This case study has some limits: it is a retrospective study with cumulative frequencies and therefore with limitations in the evaluation of the incidence of complications or mortality of GPA. Nevertheless, this is the first North African and Arabic detailed survey of the population with GPA.

CONCLUSIONS

Our study provided an overview of GPA features in Tunisia. Our patients had a distinct phenotype. Interestingly, we noticed high prevalence of pleural involvement, lymph node enlargement, sensorimotor neuropathy and ureter stenosis. ENT symptoms were less frequent as inaugural presentation.

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