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Thoracic Involvement in Polyangiitis Granulomatosis: A Moroccan Series of 21 Case

H. Benjelloun [a], H. Anniche [a*], W. Jalloul [a], N. Zaghba [a], K. Chaanoun [a] and N. Yassine [a]

[a] Faculty of Medicine and Pharmacy, University Hassan II, Hospital Ibn Rochd, Casablanca, Morocco.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Granulomatosis with polyangiitis, formerly known as Wegener's disease, is a severe systemic necrotizing vasculitis, associating an inflammation of the vascular wall with a peri and extravascular granulomatosis. It is a rare disease that affects small vessels.it is classically translated by an otorhinolaryngological, respiratory and renal involvement. Other systemic manifestations of vasculitis may also be present.of slow evolution, the disease is often misleading and difficult to diagnose.The aim of our work is the analysis of the clinico-radiological thoracic and extra-thoracic manifestations, as well as the therapeutic and evolutionary profile in a retrospective study of a series of 22 cases.

Keywords: Inflammatory; granulomatosis; vasculitis; pulmonary attiente.

1. INTRODUCTION

Granulomatosis with polyangiitis (GPA), the new term for the classic Wegener's granulomatosis, is a necrotizing vasculitis that combines inflammation of the vascular wall of small vessels with peri- and extravascular granulomatosis. Clinically, in its complete form, GPA is characterized by ENT signs, pulmonary and renal involvement, and other systemic manifestations may occur. GPA is accompanied by the positivity of cytoplasmic ANCA, in about 90% of diffuse forms and 50% of localized forms, which are directed against proteinase 3 in the

**Corresponding author: E-mail: halimaanniche4@gmail.com;*

vast majority of cases. GPA is a serious disease, fatal in the absence of treatment. However, current therapies, based on the combination of corticosteroids and cyclophosphamide or rituximab, make it possible to control the evolution and to cure it in most cases, even if relapses remain frequent.

2. PATIENTS AND METHODS

This is a retrospective descriptive and analytical study of 21 cases of thoracic involvement during GPA collected in the department of respiratory diseases of the Ibn Rochd University Hospital of Casablanca, during a 17-year period from January 2004 to January 2022. All patients who met the ACR (1990) criteria for the diagnosis of GPA, and/or who had a concordant immunological work-up, and who presented specific respiratory manifestations of the disease were included in our study.

3. RESULTS

These were 21 patients whose average âge was 48 years, with extrêmes ranging from 17 to 72 years, and a slight female predominance .The time between the first symptom and consultation was variable from one patient to another, especially since most of the patients were of low socioeconomic level .This one was on average 58 days with extremes ranging from 15 days to 8 months . All our patients presented functional respiratory signs, notably dyspnea in 17 (82%) cases, chest pain in 13 (61%) cases, hemoptysis in 12 (58%) cases, bronchial syndrome in 11 (55%) cases, and dry cough in 3 (14%) cases. The extra-respiratory functional signs were dominated by epistaxis in 7 (33%) cases, macroscopic hematuria in 3 (14%) cases, and acute headache in 2 (9%) cases. The physical examination revealed a performance status between 3 and 4 in 17 cases. The chest examination revealed a syndrome of liquid effusion in 3 (14%) cases, crepitus in 4 (19%) cases, snoring in 3 (14%) cases. Cutaneous and mucosal signs were noted in the form of ulcerative necrotic purpura in 2 (9%) cases, a reddish-purple placard on both lower limbs, pigmented scarring lesions on the face and both hands, papulo-nodular lesions on both lower limbs and both hands in 1 (4%) case each. ENT examination with rhinoscopy was performed in 13 (61%) patients showing normal pituitary mucosa in 7 (40%) cases, polyploid pituitary mucosa in 4 (20%) cases, and purulent rhinorrhea with granulomatous inflammatory nasal mucosa and a very large hypertrophy of the middle turbinates in 2 (20%) cases Neurological examination revealed a peripheral neurogenic syndrome, and flaccid areflexic tetraplegia in all 4 limbs in one case each. Chest radiography was the first-line examination in all our patients. Reticulo-micronodular images and bilateral excavated opacities were the most frequent findings in 9 (42%) and 6 (28%) cases respectively. The thoracic CT scan was performed in 18 patients and showed foci of alveolar condensation in 9 (42%) cases, diffuse ground glass in 8 (38%) cases, bilateral nodules and micronodules in 5 (22%) cases, mediastinal adenopathies in 4 (21%) cases, bilateral excavated images in 4 (19%) cases, right pleurisy and right inferior lobar tissue process in one case each. Flexible bronchoscopy, performed in 17 (81%) patients, showed diffuse inflammation in all cases, thickening of the spurs in 11 (64%) cases, and traces of bleeding in 3 (17%) cases, active bleeding from all orifices in 1 (5%) case.Bronchoalveolar lavage was performed in 14 (66%) patients.Macroscopically, the bronchoalveolar fluid was uniformly hemorrhagic in 5 (35%) patients. Microscopically, it was predominantly macrophagic with the presence of unquantified siderophages and a Golde score < 20 in 12 (85%) patients. Pathological examination of bronchial biopsies, both staged and transbronchial, revealed chronic non-specific inflammatory changes in 17 (100%) patients, non-necrotizing granulomatous inflammation in 2 (11%) patients.Thoracoscopic lung biopsy, performed in 1 (4%) patient was in favor of a morphological aspect of small vessel vasculitis. Renal biopsy, performed in 9 (42%) patients, revealed extracapillary glomerulonephritis with granulomatous lesions related to vasculitis in 4 (44%) patients, chronic glomerular and tubulointerstitial lesions without specific deposits in immunofluorescence in 2 (22%) patients Chronic pyelonephritis with granulomatous foci and epithelioid granulomas, chronic agranular nephropathy and extra-membranous glomerulonephritis without vasculitis lesions in one case each. Nasal biopsy, performed in 11 (52%) patients, showed a histological aspect suggestive of Wegener's granulomatosis in 4 (36%) patients. Skin biopsy in 5 (23%) patients showed leukocytoclastic vasculitis in 3 (60%) patients and necrotizing vasculitis in 1 (20%) patient. An immunological workup, performed in 19 (90%) patients, revealed the positivity of diffuse cytoplasmic neutrophil antibodies (c-ANCA) in 17 (89%) patients. Microcytic hypochromic anemia in 13

(61%) cases, PNN hyperleukocytosis in 14 (66%) cases, renal failure in 12 (57%) cases, accelerated sedimentation rate (ESR) in 13 (61%) cases, and elevated C-reactive protein (CRP) in 12 (57%). The GeneXpert in the bronchial aspiration fluid was positive in 1 (4%) case.therapeutically, all our patients benefited from a symptomatic treatment made of Hemostatic in case of hemoptysis, oxygen therapy, antibiotics and analgesics. The basic treatment, started after a negative infectious assessment, was based on a combination of corticotherapy (1 bolus of methylprednisolone at a rate of 15 mg/kg/day for 3 days as an initial treatment, followed by oral prednisolone at a rate of 1 mg/kg/day), and immunosuppressive drugs (1 bolus of cyclophosphamide at a rate of 600 mg/m2 every 2 weeks for 6 weeks, then every 3 weeks until remission). Anti-bacillary treatment was started in 1 (4%) case for a duration of 6 months. Given the poor prognosis of this pathology, we deplored 11 (55%) cases of death, 5 of which were due to acute respiratory failure, 4 due to a probable state of shock, and 2 due to a hemoptysis of lightning. Five patients were lost to follow-up after receiving 3 boluses of oral corticosteroids and 2, 3, and 12 boluses of Cyclophosphamide and 150 mg of Azathioprine in three doses per day. Five patients are still alive after one year.

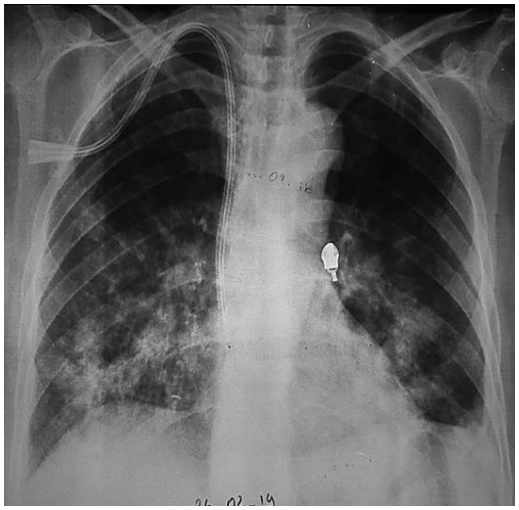

Fig. 1. Frontal chest radiograph showing bilateral excavated opacities with filling of the left costodiaphragmatic

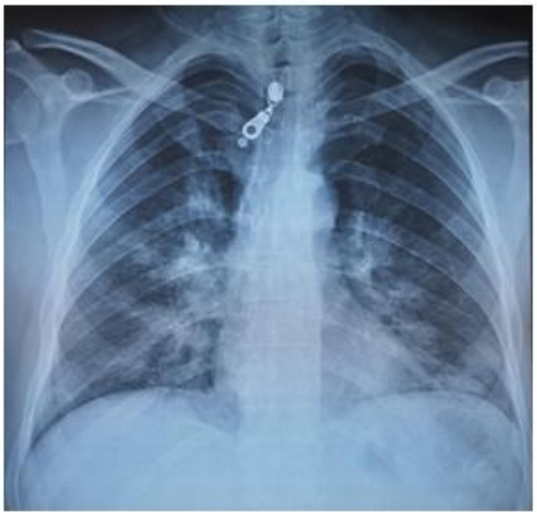

Fig. 2. Inter-hilo-basal infiltrates and alveolar-type opacities

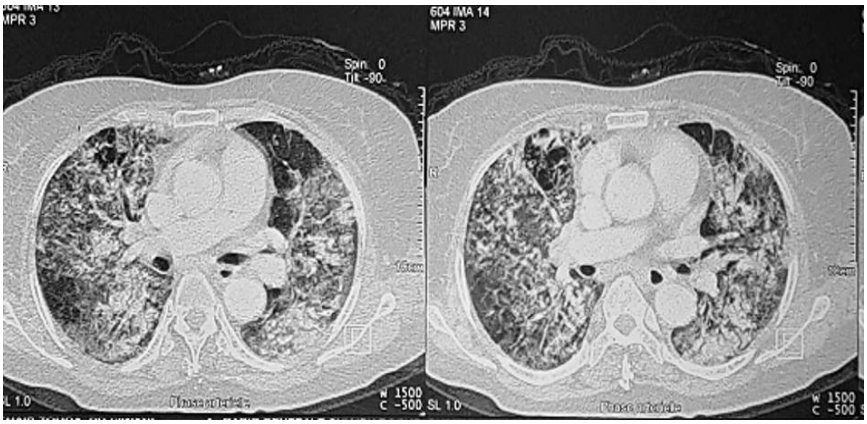

Fig. 3. Scans showing a diffuse ground-glass appearance in both lung fields associated with diffuse bilateral alveolar condensation

Fig. 4. Hemorrhagic appearance of bronchoalveolar fluid

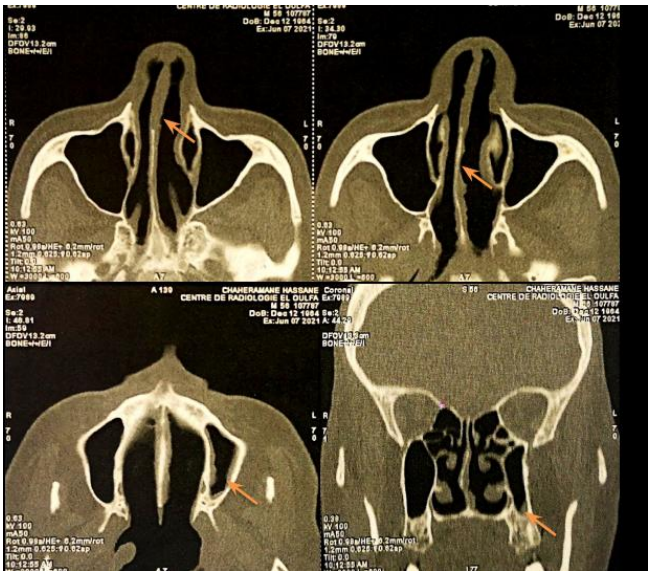

Fig. 5. CT scan of the sinuses in favor of erosion and bone demineralization of the middle and lower turbinates and the nasal septum, and diffuse nodular mucosal thickening of the sinuses in favor of granulomatosis

4. DISCUSSION

GPA is a severe systemic disease of undetermined origin characterized by its triple tropism (ENT, pulmonary and renal). It is a rare disease with a prevalence of approximately 3/100,000 inhabitants [1,2], with a greater frequency in the Nordic countries. GPA affects both sexes. The average age is 45 years. The various series in the literature show an average diagnostic delay of five to 13 months after the onset of the first symptoms [3] . Respiratory involvement in GPA is encountered in more than 80% of cases [4,5]. In our study, respiratory involvement was revealing of the disease in all our patients, and the pulmonary signs are non-specific: cough, dyspnea, chest pain, hemoptysis [6,7]. Chest imaging shows nodules, single or bilateral, single or multiple, excavated in half of the cases, diffuse, bilateral, asymmetric, low density infiltrates (ground glass), particularly suggestive of intra-alveolar hemorrhage, condensation foci, and pseudo-tumoral granulomatous pulmonary masses. Bronchial fibroscopy may reveal inflammatory conditions or stenoses as a consequence of granulomatosis; however, the cost-effectiveness of endoscopic biopsies is low. Respiratory involvement in granulomatosis with polyangiitis can have several presentations, which can be isolated or associated with each other.Parenchymal involvement in the form of pulmonary nodules, which are the most characteristic lesions of the disease, and are found in 40 to 66% of patients, which is in line with the results of our study.Vascular involvement in the form of intra-alveolar haemorrhage (IAH), which, together with renal involvement, constitutes the pneumo-renal syndrome. The diagnosis of IAH is confirmed in the alveolar lavage when it comes back uniformly red or pinkish, with a Perls stain showing more than 30% of siderophages and/or the Golde score is higher than 100 [8]. There is also an increased risk of pulmonary embolism. Tracheobronchial involvement is frequent, with lesions at all levels, such as mucosal thickening, sometimes calcified, and endobronchial masses or strictures. Pleural involvement is only related to the disease in 10% of cases, as it is often of infectious or mechanical origin. ENT manifestations are the most frequent during the course of GPA, and are noted in 70 to 100% of patients, often revealing the disease [9]. They often include persistent nasal obstruction, rhinitis which may be hemorrhagic and/or crusty, repeated epistaxis, otitis media and/or hypoacusis and recurrent sinusitis. More rarely, more destructive lesions can be observed, such as perforation of the nasal septum, the palate and/or the auricle, and chondritis of the facial cartilages, which can lead to nasal deformation with an appearance known as a "hoofed" or "pot-bellied" nasal saddle. Sinus bone lysis may reach the orbital framework and be accompanied by the development of granulomatous inflammatory pseudotumors, responsible for exophthalmos and/or ophthalmoplegia [3,7]. The CT scan of the sinuses may show uni or bilateral sinusitis, bone destruction and/or lysis of the nasal cartilages. Naso-sinusal biopsies show non-specific variations. It is a rapidly progressive renal failure with histologically an extra-capillary glomerulonephritis. Immunofluorescence is negative. The search for hematuria and proteinuria is essential at the time of diagnosis and at each monitoring visit. If not detected or treated in time, it can lead to severe renal failure. It is important to treat it quickly because partial or total reversibility can be obtained with treatment. Renal failure can also have other origins such as ureteral stenosis responsible for uni- or bilateral hydronephrosis or an iatrogenic cause [4].Among the other manifestations of GPA, we cite the involvement of the nervous system which is observed in about one third of patients. In our study, we found neurological involvement in 2 (18%) cases.10 to 50% of patients have skin lesions.Ocular and/or orbital involvement is frequent, reported in 14 to 60% of patients. Cardiac involvement is relatively rare, described in an average of 6% of patients. Gastrointestinal involvement concerns 5 to 11% of patients.Cases of mastitis, mammary involvement and uterine localization have been described.Cases of GPA appearing or aggravated during pregnancy, postpartum or postabortion have been reported.Thromboembolic manifestations are frequent during GPA [2,4]. Thromboembolic events are frequent in GPA [2,4] and rarely reveal the disease. In men, several cases of granulomatous prostate involvement have been described, as well as orchitis and/or urethritis and/or penile ulcerations.GPA is accompanied by an essential element in the diagnosis and monitoring of the disease: the positivity of ANCA, of diffuse cytoplasmic fluorescence, directed against proteinase 3 in 75% of cases and much more rarely against myeloperoxidase. They are present in about 90% of diffuse forms and 50% of localized forms of the disease. They are very specific and therefore have diagnostic value. Anatomically, GPA is characterized by ischemic necrosis in the form of a geography map, which

results in the formation of amicrobial abscesses and polymorphic granulomatosis, which associates polynuclear cells, lymphocytes and multinucleated giant cells. In total, the presence of 2 of the 4 criteria (Nasal or oral inflammation: epistaxis, painful oral or facial ulcerations; Chest x-ray abnormalities:nodules, caverns, fixed infiltrates;Urinary sediment abnormalities: microscopic hematuria or cylinders; Granulomatous inflammation on biopsy in the wall and/ of arteries or arterioles) of the american college of rheumatology (ACR) 1990 classification allows classification as granulomatosis with polyangiitis with a sensitivity of 88.2% and a specificity of 92% [1]. The basic treatment of GPA is currently based on a combination of corticosteroids and certain immunosuppressants, according to a fairly well-coded sequential scheme, consisting of an attack (or induction) treatment, followed by a maintenance (or remission maintenance) treatment [10], the optimal duration of which is not yet fully established. Induction therapy aims to put patients into remission when the diagnosis is made in the acute phase of the disease.Corticosteroids can rapidly improve some symptoms.They are usually used as intravenous boluses (15 mg/kg/day of Methylprednisolone for 3 days) followed by oral corticosteroids at a dose of 1 mg/kg/day of Prednisone, which is gradually tapered over several months. It is desirable to rapidly reduce the dose of corticosteroids in order to reach a half-dose after 1 to 3 months. Cyclophosphamide can be used either as an intravenous bolus (500 to 700 mg/m2 every 2 to 3 weeks) or in its oral form (2 mg/kg/d) until remission is achieved. Cyclophosphamide, in combination with corticosteroid therapy, allows prolonged remissions. Rituximab is prescribed in this indication at the usual dose of 375 mg/m2 per week for a total duration of 4 weeks. This molecule is probably less toxic than alkylating agents such as Cyclophosphamide. Maintenance therapy allows to maintain remission of the disease and to prevent relapse. Prolonged use of oral Cyclophosphamide after remission has been achieved limits the relapse rate to 13% at 5 years. On the other hand, continuation of intravenous Cyclophosphamide is not as effective, since the associated relapse rate is 59% at 5 years. Other less toxic immunosuppressants should therefore be prescribed as maintenance therapy, as a relay to Cyclophosphamide, as soon as remission is achieved. The choice today is mainly between 3 molecules: Azathioprine, Methotrexate and Mycophenolate mofetil (MMF) [11,12]. Untreated, GPA has a 1-year mortality rate of about 70%; under treatment, remission is obtained in more than 80% of cases. Relapses are frequent and occur in more than 50% of cases. Despite this, the survival rate reaches 75% at 10 years; ENT involvement is associated with a better vital prognosis but with a risk of relapse. A prognostic score FFS (Five Factor Score) has been proposed [13], the updated version of which also applies to GPA . It takes into account 5 events associated with excess mortality: the existence of an age greater than 65 years, specific cardiomyopathy, gastrointestinal events, renal failure defined by a stabilized creatinine level greater than 150 mol/l and the absence of ENT events.Each item scoring for one point. Nevertheless, if the FFS informs on the prognosis of GPA, it does not condition the treatment, as for other necrotizing vasculitides [12].

5. CONCLUSION

GPA is a rare, severe, chronic, and frequently recurrent vasculitis. The involvement of the respiratory system is polymorphic. Any functional sign associated with chronic rhino-sinus symptoms, and in front of any pneumo-renal syndrome, the diagnosis of GPA must be evoked, and retained on 2 of the 4 criteria of the classification of the American college of rheumatology (ACR) 1990. However, thanks to an adapted and prolonged treatment based on the association of corticoids with immunosuppressants, the prognosis has improved. The survival rate of the disease currently reaches 75% at 10 years. One of the major problems is related to the occurrence of side effects of the treatments, the severity and frequency of which are often the consequence of a prolongation of the treatment that is difficult to avoid [14-17].

CONSENT

It’s not applicable.

ETHICAL APPROVAL

It’s not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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