"Extra-Cranial" Manifestations of Giant Cell Arteritis

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1. Introduction

Giant cell arteritis (GCA) is a primitive systemic vasculitis related to a sub-acute inflammatory panarteritis, histologically characterized by segmentary and plurifocal damage, with giant cells and destruction of the internal elastic lamina. GCA involves large and medium sized vessels in subjects over 50, particularly between 75 and 85, and is more common in women (7:3sex-ratio). This arteritis preferentially affects the external carotid and its branches, and more specifically the superficial temporal artery, which explains the usual clinical signs of the disease which are headaches, tenderness and sensitivity of the scalp, painful thickening of the temporal arteries associated with absence of pulsation, and jaw claudication. However, this description of GCA was enriched in 1938 by the first observations of « extra-cranial » manifestations.
A diagnosis of GCA is usually suspected in the elderly subject on the association of focal signs of arteritis prevailing in the head, with a more or less febrile alteration of the general health condition and an inflammatory syndrome. The classification criteria of GCA most used are those of the American College of Rheumatology and which date back to 1990.
Nevertheless, GCA, because of the potential ubiquity of the pathological process, can occur in atypical forms, which renders the etiological approach more complex. The risk is therefore a delay in diagnosis which can jeopardize the prognosis of this disease.
In this chapter, we will approach different atypical aspects of GCA, which can all be inaugural of the disease, whose prognosis will depend on their early recognition. They include aorta and its main branches involvement except arteritis of the branches of the external carotid artery, heart, lung, neurologic, genital and musculoskeletal manifestations.

2. Aortitis and limb arteritis in giant cell arteritis

The diagnosis of GCA is based on clinical, biological and histological elements described in the classification criteria defined by ACR in 1990. The diagnosis is evident in the case of clinical manifestations relative to the involvement of the external carotid branches. However, temporal arteritis is not systematic, and involvement of the aorta and its main branches may be isolated. In this case, diagnosis is complicated by a clinical presentation which is often poor and non-specific, and by the difficulty of obtaining histological proof; the new methods of imagery that we are going to describe can then be useful in diagnostic.

GCA is one of the three main causes of inflammatory aortitis, besides Takayasu's arteritis and Behçet's disease (Launay & Hachulla, 2003). However, involvement of the large vessels, and specifically the aorta, is often little known. Data from series of autopsies evaluate the frequency of aortic involvement up to 70 % during GCA. In the series of Hervé et al. (2006), the frequency of thoracic and abdominal involvement diagnosed by Computer Tomography (CT) scan were close (73 and 82 % respectively); moreover, concomitant thoracic and abdominal involvement was frequent, since it concerned 55 % of the patients. In the study of Agard et al. (2009), 22 patients and 22 controls were screened by CT scan for aortic involvement. Thickening of the aortic wall was more frequent among patients than controls (45.4% versus 13.6%; P 0.02). Aortic thickening was located on the ascending part of the thoracic aorta in 22.7% of the patients, with no evidence of thickening in the controls (P 0.05). Thickening of the abdominal aortic wall was noted in 27.3% of the patients and none of the controls (P 0.02).

Aortic involvement may be the mode of revelation of the disease. It can also occur during corticosteroid decrease or withdrawal in patients carrying a known GCA. The clinical presentation can be limited to a febrile syndrome, an alteration of the general state of health and an inflammatory syndrome. The existence of inflammatory back pains is not systematic. The clinical diagnosis of aortic lesion is often difficult and late in GCA, due to the long latency of this involvement and the absence of clinical presentation (Bossert, 2010). Aortic lesions represent yet another major cause of morbidity and mortality during GCA. They can actually be complicated by aneurisms, aortic dissections and less frequently stenosis. Increased frequency of aortic aneurisms during GCA is established and they expose the patient to the risk of potentially fatal accidents (embol, dissection). In 1995, Evans et al. showed on a retrospective series of 96 patients suffering from GCA a risk 17.3 times higher of developing a thoracic aneurism and 2.4 times higher of developing an isolated abdominal aneurism, in comparison with the population of the same age and sex. In 2003, out of a cohort of 168 patients with GCA, Nuenninghoff et al. (2003) found 30 cases (18 %) of aortic aneurisms, 18 of them in the chest; nine were complicated by aortic dissection, with seven deaths.

Arterial involvement in GCA is not limited only to the thoracic or abdominal aorta. The GCA may be revealed by a lesion in the upper or lower limbs.

Upper and/or lower limb inflammatory arteritis during GCA is not exceptional occurring in 3 to 16% of patients. It is rarely reported in the literature but is probably under-estimated as it is often low symptomatic (Assie & Marie, 2011).

Hamrin et al. were among the first authors as early as 1965 to draw attention to the possibility of "extra-cranial" arterial involvement through the existence of arterial murmurs on the trajectories of the limb arteries. It must not be neglected by the clinicians managing these patients due to the severe ischemic complications that it can trigger, amputation being necessary in 5.6 to 15.8 % of cases (Assie & Marie, 2011).

In the review of 318 cases published by Assie and Marie (2011), it can be noted that the patients present more often a lesion in the upper (63.1 %) than in the lower limbs (32.2 %); with concomitant involvement of both the upper and lower limbs arteries in 4.7 %. It was also observed that the arterial sites involved are in order of frequency:

- subclavian arteries (53.2 %), axillary arteries (37.3 %), brachial arteries (24 %) ;
- iliac arteries (0.43 %), common femoral arteries (2.6 %), superficial femoral arteries (24.9 %), deep femoral arteries (10.3 %), popliteal arteries (16.3 %), tibio-peroneal trunk (1.3 %), and tibial arteries.

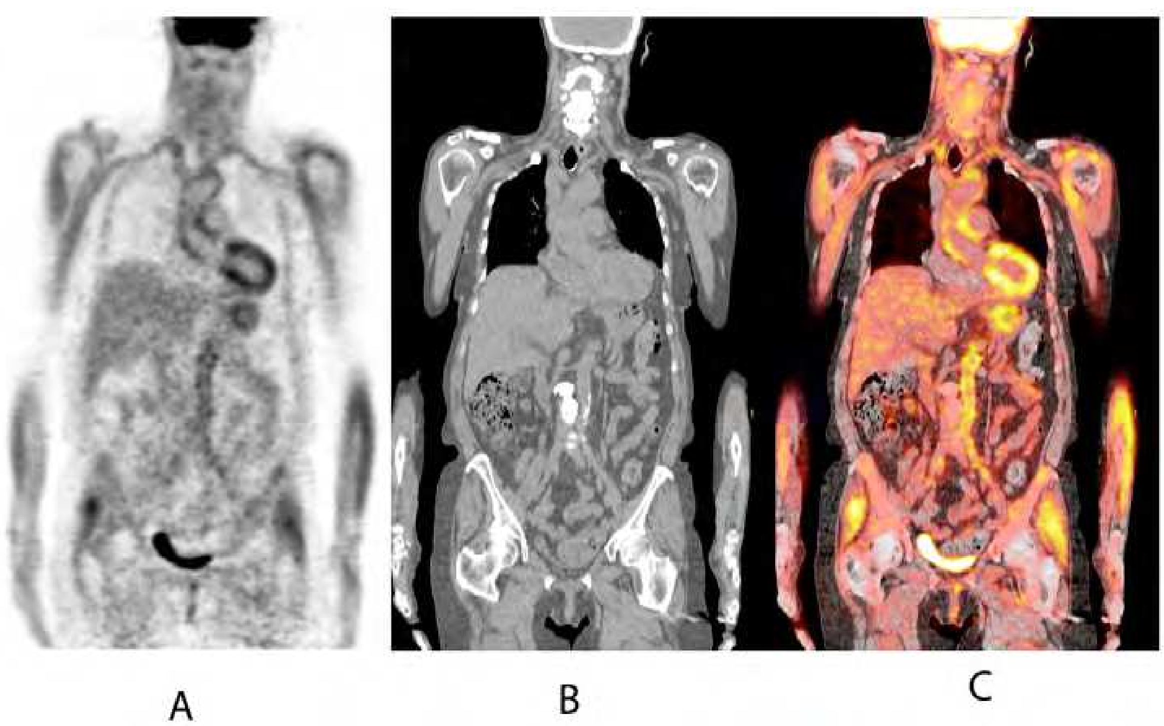
If the upper and/or lower limb arterial involvement can be the mode of revelation of GCA, it can also occur during corticosteroid decrease or withdrawal in patients with a known GCA. In the observation by Skopinski et al. (1997), for four women and one man, aged from 67 to 77, the mode of revelation was intermittent claudication of an upper limb in three cases and bilateral Raynaud's syndrome in one case. The discovery was accidental in one case (the general practitioner was anable to measure blood pressure). In all cases there was an absence of peripheral pulse, and it was impossible to measure blood pressure on the side involved. All the patients had a biological inflammatory syndrome. Arteriography showed that all the patients had long and tight stenosis on the subclavian, axillary and humeral arteries. The biopsy of the temporal artery, carried out in all five cases, was positive in three. A surgical act of revascularisation was only necessary once. Evolution of the clinical symptomatology and the inflammatory syndrome was constantly favourable under prednisone. Furthermore Tazi et al.(1997) reported the case of a woman of 67 with no risk factors for atheroma, hospitalised for lower limbs ischemia relative to bilateral occlusion of the superficial femoral arteries. The femoral artery biopsy did not reveal any thrombosis but showed the inflammatory nature of the lesion confirming the diagnosis of GCA. Upper and/or lower limb arterial involvement occurs more frequently in women; in the literature (Assie & Marie, 2011), 58.8 % of the patients were women with a median age of 67. The clinical manifestations included intermittent claudication of a limb (68.6 %), decrease in pulse or absence of a peripheral, limb ischemia (17.9 %), even gangrene of a limb/toe/finger (6.4 %). However limb arterial involvement does not always have a clinical expression in the early stages. Thus involvement must not be neglected by physicians managing these patients due to the severe ischemic complications it can trigger.

In this context, aortitis appears frequent in patients with an upper and/or lower limb arterial involvement complicating a GCA. Weyand and Goronzy (1999) noted an aortitis in 10 to 15 % of these patients. Likewise, in a recent series, an aortic localization was associated with a limb arterial involvement in up to 68.9 % of the cases (Assie et al.2011). In view of the potential gravity of aortic lesions, it would appear justified to carry out a systematic exploration of the aorta and its branches to look for an aortitis in patients presenting a GCA. Interestingly, in the work of Assie et al.(2011), headaches (25 % vs. 77 %), jaw claudication (11 % vs. 35 %), tenderness and sensitivity of the scalp (8 % vs. 67 %) and a positive temporal artery biopsy (69 % vs. 95 %) were all less frequent in the group carrying an upper and/or lower limb arterial involvement than in that who had none. Likewise, Hervé et al.(2006) found less frequent usual inaugural signs of GCA in cases of aortitis. Brack et al. (1999) mentioned that the group of patients carrying a large vessel involvement, compared with those with a predominant cephalic involvement, were younger (66 vs 72) and had less often the classical signs of GCA (headaches, jaw claudication, visual disorders).

Different complementary non-invasive vascular examinations can be carried out to search for a limb or aortic arterial involvement. Arterial Doppler ultrasound is a simple non-invasive examination for studying large arteries in patients. In GCA, arterial inflammation is determined by a circular thickening of decreased echogenicity of the vascular wall around the arterial light (halo of decreased echogenicity). Moreover, studies have found a correlation between the type and the seat of the arterial lesions revealed by arterial Doppler ultrasound and angiography, which confirm the high sensitivity of this examination in detecting upper and/or lower limb arterial involvement in GCA (Schmidt et al. 2005; Agard et al.2009).

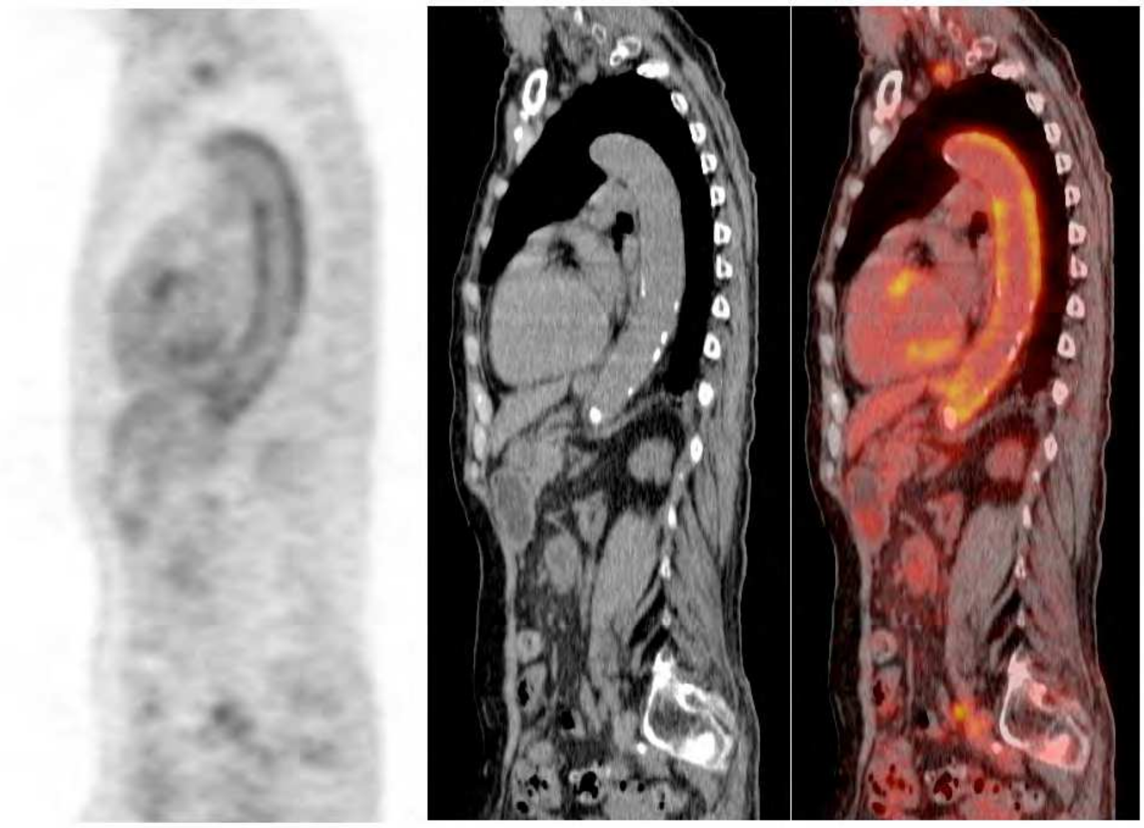
On the other hand, arterial Doppler ultrasound presents a limited interest for following up arterial involvement in the patients treated; the thickening of the vascular wall would appear to persist under corticosteroids, which complicates the correlation between the ultrasound data and GCA activity. Angioscan is useful as an examination to detect aortic involvement and limb arterial involvement, and it has the added advantage of being more available and shorter than the MRI angiography. Therefore, Agard et al.(2009) and Hervé et al. (2006) highlighted the diagnostic interest of the angioscan for the diagnosis of inflammatory aortitis in patients suffering from a GCA, as this examination makes it possible to visualize directly the suggestive anomalies of the aortic wall (circumferential parietal thickening, regular and homogeneous, more than 3 mm thick). In addition to this, we can note the interest of the angioscan for the follow-up of GCA aortitis (Hervé et al. 2006).

Lastly positron emission tomography (PET) with 18 FDG, a noninvasive metabolic imaging modality that is well-suited to the assessment of activity and extent of large vessel vasculitis, also appears to be a promising technique. Contrary to the previous radiological examinations, it can detect vasculitis lesions all over the body and it is more sensitive to show inflammatory vascular wall process (Belhocine et al 2002 ;Liozon et al.2010) (figures 1-3); these data suggest the potential clinical interest of the PET in the vascular disease activity, extension and follow-up of patients with GCA (figure 4).



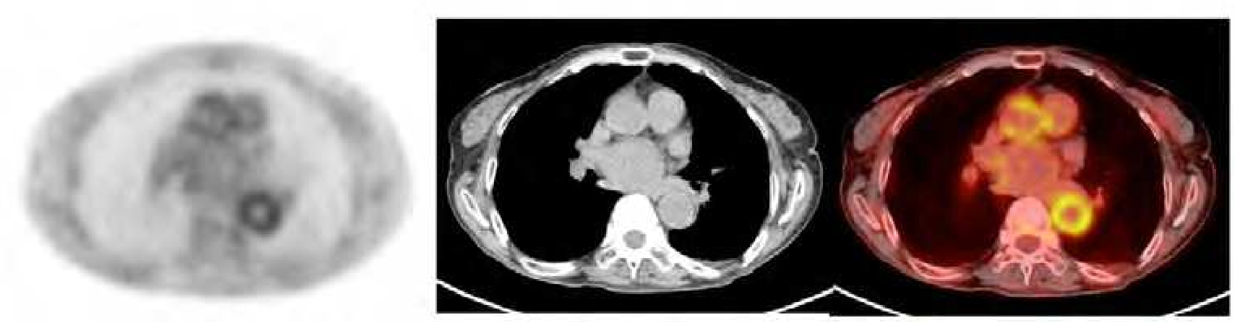
A: PET image.
B: CT-scan image.
C: images fused PET and CT-scan.

Fig. 1. Coronal view of Positron Emission Tomography (PET) showing hyper metabolism of the thoracic and abdominal aorta walls extending to the subclavian arteries indicating aortitis.



A B C

Fig. 2. Sagittal view of inflammation of the descending thoracic aorta (A : PET, B: CT-scan, C: fusion of the PET and CT-scan images).

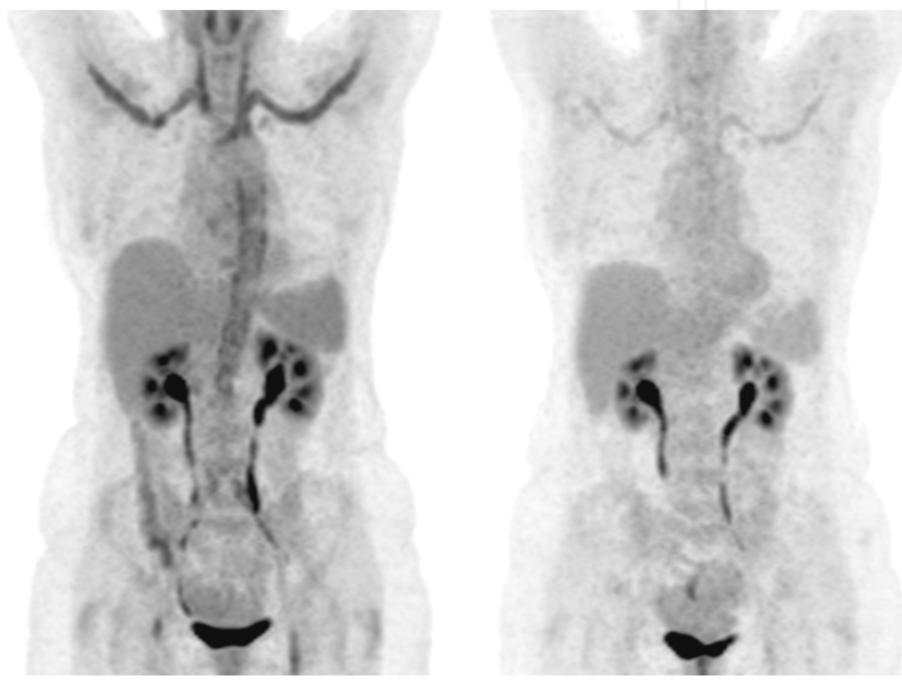


A B C

Fig. 3. Axial view showing hyper metabolism of the ascending and descending wall of thoracic aorta, indicating aortitis (A: PET, B: CT scan, C: images fused PET-CT).

One of the limits of PET is its availability and its spatial resolution which does not make it possible to highlight the involvement of arteries with a size of less than 4mm (Loizon et al. 2010).

The treatment of vascular lesions is the same than classical form of GCA relying on corticosteroids. The hypothesis of administration of a higher or longer dose of corticosteroids in the case of aortic and large artery involvement does not reside on any element of proof. The occurrence of thrombotic complications during GCA also leads to discussion on the interest of a treatment by antiplatelet drug or anticoagulants, whose use is not codified. Nesher et al.(2004), in a non-randomized study of 175 GCA patients, reported a reduction of the incidence of neurological ischemic complications in the group of patients treated with aspirin compared with the group which did not receive any (4 % vs. 29 %). In another series, Lee et al. (2006) also mentioned that the risk of occurrence of ischemic complications was three times higher in the group of patients who did not receive an aspirin treatment against the treated group. A few caveats, however, are necessary before one recommends that low-dose aspirin should be added as standard of care in GCA.



A B

Fig. 4. Maximal Intensity Projection (MIP) of PET showing hyper metabolism of the thoracic and abdominal aorta extending to the subclavian arteries, before (A) and after three months of steroids (B), pointing out the decrease of the inflammation of the arterial walls.

There are very few data, in the form of isolated observations only, relative to the usefulness of anticoagulants in the initial stage of GCA. For some authors, the use of anticoagulants in this indication resides on the following elements: (1) Giant cell arteritis is a granulomatous arterial disease causing sometimes very tight arterial stenosis which can be the seat of an intraluminal thrombosis; (2) the blood rates of the von Willebrand procoagulating factor are increased during GCA. At present, due to the lack of open or randomized studies having analysed the interest of anticoagulants in this context, anticoagulation cannot be recommended systematically for these patients. In practice, in the case of a severe acute ischemic limb involvement, an anticoagulant treatment is usually prescribed.

Immunosuppressive treatments have not been evaluated in these forms. The role of vasodilators remains to be determined. In the series of Benjilali et al. (2009), intravenous prostaglandins had given a good result in a patient with threatening ischemic lesions, in association with corticosteroids and anticoagulants.

To date there is no consensus for the choice of imagery and the rhythm of supervision of aortitis. The follow-up must be regular and on long-term, even after the withdrawal of corticosteroids. As certain authors suggest (Garcia et al.2008), supervision once a year by lung X-ray, transthoracic echocardiography and Doppler ultrasound of the abdominal aorta would seem to be appropriate. Thoracic-abdominal scan with injection and 3D reconstruction is also efficient in this indication (Hervé et al.2006). Lastly, PET would appear to be more interesting than CT scan to evaluate the response of the aortitis to corticosteroids; The vascular metabolic signal disappears, despite the persistence of a perivascular cuff in CT scan (Liozon et al.2010).

3. Mesenteric artery involvement

Described for the first time by Hamrin et al. in 1965, mesenteric inflammatory arteritis is rare in the course of GCA. The majority of articles do not mention GCA among the causes of mesenteric ischemia. From this point of view, analysis of the literature has enabled us to list 33 cases of mesenteric inflammatory arteritis in patients carrying GCA. In the review of the literature (Lorthior et al.2008), diagnosis of mesenteric inflammatory arteritis and GCA was concomitant in 57.6 % of the cases; in the other patients, mesenteric inflammatory arteritis appeared in the development of GCA, usually in the first three months following its diagnosis. The diagnosis of GCA mesenteric arterial lesions is often difficult due to the absence of specific clinical presentation. In all 33 cases, the patients presented: abdominal pains (97%) which were rarely characteristic of mesenteric angina (15.2 %); an occlusive syndrome (42.4 %) or a digestive haemorrhage (6.1 %), and the last patient was asymptomatic from the digestive point of view. These elements suggest that the prevalence of the mesenteric inflammatory arteritis is probably under-estimated during GCA; systematic prospective, vascular imaging studies could make it possible to determine its prevalence along with the incidence in these patients. If the final diagnosis of mesenteric inflammatory arteritis resides, in theory, on the histological examination, arterial biopsies of this kind are an invasive examination, and are not carried out in practice. Colour Doppler ultrasound is an inexpensive and easily available examination, and frequently used at the beginning. At present, the angioscan would appear to be a useful examination to objectivise mesenteric arterial involvement; this examination makes it possible to highlight directly the suggestive anomalies of the mesenteric artery wall: a regular and homogeneous (> 3 mm) thickening, a luminal stenosis and also a periarterial halo and the absence of calcification (Lorthioir et al. 2008). MRI angiography could also be useful for the diagnosis of mesenteric arterial lesion but complementary studies to assess its relevance are necessary. Lastly, PET could also be a useful diagnostic technique in this indication; however, today, it is not possible to analyse small vessels (diameter under 4 mm) with the PET (Liozon et al. 2010). At present, mesenteric arterial lesions are a major cause of morbidity and mortality in GCA. They can be complicated by chronic mesenteric ischemia, mesenteric infarcts, ischemia-related intestinal pseudotumors, or digestive perforations. Some authors (Scola et al. 2008; Sujobert et al. 2008) suggest that the prognosis of patients with only prednisone was better than that of patients who received a medico(prednisone)- surgical treatment; these data seem, partly, to be explained by the fact that the patients treated surgically presented more severe mesenteric arterial complications.

Some patients received, in association with steroids, a complementary treatment with antiplatelet drug. However, the efficiency of these treatments in the reduction of the risk of thrombosis, in patients suffering from a mesenteric giant cell arteritis, remains to be determined.

4. Pericarditis an unusual manifestation

Pericarditis during GCA is rarely reported. In the literature, we were only able to find twelve observations in 20 years (Bablekos et al. 2006; Dupond et al. 1982; Clementz et al. 1989; Garewal et al. 1981; Guillaume et al. 1991; B; Guindon et al. 2007; Preston et al. 1991; Pedro-Botet et al. 1996; Matsue et al. 2011; Moulis et al. 2010; Stanley et al. 1989 & Valstar et al. 2003). In nine of these cases, cardiac symptoms including chest pain, exertional dyspnea or pericardial fremitus were present, but in three of the cases, the pericarditis was silent and was discovered on chest X-ray anomaly (Guindon et al. 2007; Miller 1996; Pedro et al. 1996). In this observations, the classical electrocardiographic anomalies of pericarditis (PR segment depression, repolarization anomalies) are not constant and one case only has been described with signs of ultrasound tamponade which did not however necessitated drainage, the hemodynamics being stable and progression satisfactory with corticosteroids (Valstar et al. 2003).The pericarditis was inaugural of GCA in all the cases, except one incidence of a relapse after one year, following the sudden interruption of the corticosteroids (Valstar et al. 2003). In all the reported cases, the pericarditis was always regressive under corticosteroids. In the review of several cases of pericarditis during GCA carried out by Bablekos et al. (2006), the authors point out that the classical signs of the disease are only present in 2/3 of the cases and highlight the interest of looking for GCA in inflammatory « idiopathic » pericarditis in subjects over 50 (Granel et al. 2001).

The pathogenesis is not known but several hypotheses can be advanced: inflammatory cytokine storm, deposit of complex immunes, and vasculitis of the pericardial arteries or interstitial inflammatory lesion of the pericardium with or without granulomas. It is at present impossible to know its prevalence, especially as pericarditis is not symptomatic in all cases and not searched for by systematic echocardiography. Only a study to evaluate systematic echocardiography during GCA (on diagnosis or in the case of recurrence) could allow us to appreciate its real prevalence and evaluate prospectively its prognostic value.

The treatment and the progression of pericarditis do not seem to differ from those of GCA: corticosensitivity to usual doses is excellent. Even though the risk of chronicity is difficult to appreciate (monitoring in nearly all the observations published does not exceed six months), no case of progression towards constriction have been reported.

In conclusion, we wish to emphasize that pericarditis needs to be added to the list of the numerous unusual presentations of GCA. We suggest relevance of a temporal artery biopsy in elderly patients with general symptoms associated with so-called "idiopathic pericarditis" even in the absence of typical manifestations of temporal arteritis.

5. Giant cell arteritis and myocarditis

Myocarditis belongs among the other cardiac manifestations described during GCA. Classical clinical presentation of GCA is rarely associated. Temporal artery biopsy is essential in confirming the diagnosis of GCA and proposing a specific therapy, in order to prevent cardiovascular ischemic complications. Etiological research of myocarditis must lead to discuss viral or bacterial diseases in the first instance. Certain auto-immune diseases must also be suspected. GCA myocarditis physiopathology is not known and only 3 cases are reported in the literature: two cases of myopericarditis (with alteration of the left ventricular systolic ejection fraction) were described by Teixera et al. (2003)] in two female patients, respectively aged 78 and 65. It must be noted that in these two observations, at no time were any clinical signs suggestive of GCA found; biopsy of the temporal artery was motivated only by the importance of the alteration of the general health condition in an unexplained inflammatory context. A case was described in a woman of 82 hospitalised for chest pain which had for 3 months an alteration of the general health condition with a weight loss of 4 kg, bitemporal headaches and jaw claudication. Transthoracic echocardiography showed a minimal lamina of pericardial effusion, retained left ventricular systolic ejection fraction with normal coronography (Pugnet et al. 2009). Although rare and certainly under-estimated, myocarditis must be known as an expression of GCA with rapid favourable progression under treatment. The diagnosis of GCA must remain in mind faced to myocarditis of the elderly patients with healthy coronaries.

6. Coronary arteritis and giant cell arteritis

Cases of giant cell arteritis in isolated coronary arteries, resulting in myocardial infarction, are unusual and have been infrequently reported in the literature (Cohle et al 1982; Kumar et al.2002; Long-Wei et al 2007 & Saito et al 1994). It is difficult to formally relate signs of coronary heart disease to GCA. However, histologically documented observations describe a thrombosis which develops as a consequence of the coronaritis with giant cells. In most of these reports, the definite diagnosis was based on postmortem examination or on atherectomy specimen evaluation (Saito et al 1994). In the case of Long-Wei and al. (2007), the histopathological diagnosis was based on evaluation of the native heart after heart transplantation. This is the first such case mentioned in the heart transplant literature in which native heart evaluation was used to confirm this diagnosis.The involvement of the coronary arteries is associated with a very severe prognosis. These cases suggest that coronary artery giant cell arteritis should be added to the list of differential diagnoses for patients suspected of myocardial infarction due to coronary artery disease or dilated cardiomyopathy. Treatment of GCA coronaritis is not codified.

7. Respiratory manifestations

The respiratory manifestations of GCA are rare and little known. They can be associated with more typical signs of the disease, but they can also be inaugural and the cause of a delay in care. Cassarou et al. (2010) reported eight observations in 2010 which illustrate the respiratory involvement of the disease. In two observations, the pleuropulmonary manifestations were concomitant with the clinical signs of GCA. In 5 observations out of 8, the pulmonary signs were inaugural with a time lapse of 10 to 21 days before the appearance of the clinical signs suggesting GCA whereas in one observation, these last were never observed.

Cough is the most frequent respiratory manifestation of GCA; pleural effusions and alveolar-interstitial involvement were rarer. The first form of GCA presenting as a chronic cough was described in 1956 by Valleteau de Mouillac. Cough, whether accompanied by a fever or an inflammatory syndrome, can be the first sign of the disease and precede the other signs by several months. In the study by Becourt-Verlomme et al. (2001) which dealt with the inaugural signs of the disease, out of 260 patients with GCA, cough was present in

8 % of the patients. In the study by Letellier et al. (2003) which analyzed 285 patients with GCA, 57 patients (20 %) presented a dry cough with a prolonged fever and this symptom was inaugural in 22 of them (8 %).The cough is irritative, sleep-depriving, and resists symptomatic treatment. After having eliminated the most frequent causes of chronic cough, the age and the importance of the inflammatory syndrome should suggest GCA among the diagnosis hypotheses. To illustrate this involvement, Kassem et al (2010) report the observation of a woman of 70 hospitalized for a dry cough developing over three months, associated secondarily with fever and loss of weight. She had no other functional signs, the clinical examination showed no particularities and it had been identified as a biological inflammatory syndrome. A lung, sinus or digestive pathology was looked for but the chest abdomen pelvis scan was considered as normal. Bronchial fibroscopy found a congestive bronchial mucous with no endoluminal lesions. Taking age into consideration, the alteration of the general state of health and unexplained inflammatory syndrome, a biopsy of the temporal artery was carried out whose histological analysis was characteristic of GCA. The cause of cough in GCA has not been formally identified: it could be related to a pharyngeal involvement whose vascularisation depends on the internal maxillary artery, it could be secondary to an irritation of the cough-exciting centers located in the airways, the diaphragm or the esophagus from the arterial inflammation and finally cough may also be a sign of inflammatory lung involvement which may affect the pulmonary arteries, lung parenchyma and pleura. The evolution of the cough is parallel to that of the disease, and regresses rapidly under steroids with possibility of relapse during decrease or withdrawal of the treatment.

Cases of pulmonary embolism related to GCA are exceptional in the literature (Andrès et al. 2003; Chassagne et al. 1995; Landrin et al. 1997 & Radhamanohar et al. 1991). Chassagne et al (1995) report the case of a woman of 86 with a biopsy proven GCA with a clinical and biological rapid favorable outcome under steroids. She was later hospitalized for febrile dyspnea with cough which revealed pulmonary lesions resulting in a lung infarction with excavation with partial thrombosis of the left pulmonary artery. The favorable development of the symptoms was rapid and durable with an increase in the dosage of steroids (with no associated anticoagulant treatment) which strengthened the hypothesis of an inflammatory thrombosis of the pulmonary artery. In the case reported by Andrès et al. (2003), thrombophilia tests (antithrombin, proteins C and S, factor V Leiden, antiphospholipids and circulating anticoagulant) were negative as was the search for deep vein thrombosis. The post-mortem histological examination revealed a giant cell arteritis infiltrating the three wall linings of the artery with regards to the thrombus.

In the literature, pleural effusion may be unilateral or bilateral, of mild to moderate abundance, generally well-tolerated and not very symptomatic. It may be isolated or associated with a pericardial effusion and sometimes be inaugural of the disease, and render diagnosis difficult (Valstar et al. 2003). The analysis of the liquid is reported around ten times in the literature; exsudative, sterile and with a cellularity of 600 to 3200 elements/mm^3 with a predominance of either neutrophils or lymphocytes (Colnot 1996.; Deraedt et al. 1994 & Marie et al. 2004). The physiopathology of the pleural involvement is not known. Blind pleural biopsies report a non-specific inflammatory reaction or a hyperplasia of mesothelial cells in inflammatory nodules (Colnot 1996). Examination of the pleura is, particularly in histology, more profitable for eliminating differential infectious and neoplastic diagnosis than for confirming GCA. The corticosensitivity of the pleural involvement is specific to the

disease with rapid regression of the effusions, and sometimes total regression in a few days (Colnot 1996.; Deraedt et al. 1994 & Marie et al. 2004).
Parenchymal pulmonary involvement is rare and described inaugurally for a relapse of the disease after reduction or withdrawal of corticosteroids. It is often accompanied by cough but may also be discovered fortuitously in imagery. In practice, the lesions are probably under-diagnosed and under-reported, the cases described in the literature being old ones. The interstitial involvement is predominant of reticulated or reticulo-micronodular type with predominance of the basal type (Karam & Fulmer 1982). Macronodular involvement (Bradley et al. 1984) can take a single or multiple pseudotumoral aspect, sometimes excavated, and leads to discussion on neoplastic aetiology, rheumatoid nodules, infectious (tuberculosis, nocardiosis) or inflammatory (Wegener) granulomatosis. Bronchial fibroscopy and bronchoalveolar lavage play a major role in the bacteriological investigation and the search for a bronchial neoplasia when there are radiological anomalies. On the other hand, they do not supply any diagnostic specificity: the macroscopic aspect shows an inflammatory bronchitis, the cytology of the bronchoalveolar lavage is polymorphic with macrophage predominance in some observations or a lymphocytic alveolitis. Diagnostic procedure of the biopsies carried out during the bronchial fibroscopy is limited. In the observations of Cassarou et al. (2010), the biopsies revealed a non-specific inflammation. The observations of Cassarou et al. (2010) also illustrate well certain problems in diagnosing the respiratory forms of GCA: when lung involvement precedes, sometimes by a few weeks, the clinical signs of GCA and when the histology of the temporal artery is not typical or when it is negative. The differential diagnosis may be difficult with other small and medium sized vessel vasculitis with a much more frequent pulmonary involvement, especially as overlaps were reported between GCA and Churg-Strauss syndrome (Vidal et al. 1992), microscopic polyangitis, periarteritis nodosa (Godeau et al. 1984) or Wegener's disease (Astudillo et al. 2008). A GCA preceding a Wegener's disease by a few years has also been reported (Garrouste et al. 2008). In the eight observations reported by Cassarou et al. (2010), the clinical and radiological lung involvement is sensitive to corticosteroids with no relapse observed. In the same way, Carli et al. (2001) report 2 cases of scattered multiple pulmonary nodules in a context which was suggestive of GCA and totally reversible under corticosteroids after searches for neoplasia have given a negative result.
The knowledge of these different respiratory manifestations during GCA (persistent cough, nodules, pleural effusion) is useful for the clinician. It helps him in prescribing non invasive investigations or even a presumptive steroids therapy, in an often old and weakened patient.

8. Neurologic manifestations

Cerebral vascular accidents (CVA) were reported in 3 to 6 % of cases (Nesher et al. 2000) but have never revealed GCA. Central nervous system findings in GCA are the result of thrombosis of the carotid or vertebral arteries, rather than of a primary neurogenic process or intracranial arteritis. GCA affects vessels that contain, internal elastic lamina. As intracranial vessels lose their internal elastic lamina 5 mm beyond the point of dural perforation, more distal intracranial arteritis is rare. In fact, clinical and pathologic findings suggest that these ischemic events are due to involvement of extradural vertebral and carotid arteries with high-grade stenosis or occlusion rather than intracranial vasculitis. Salvarani et al. (2006) confirm that obstruction and occlusion of internal carotid and/or vertebral arteries are the most frequent causes of cerebrovascular ischemic events in patients with GCA. Involvement of intracranial/intradural arteries in patients with GCA is a rare event and appears to represent a subset of GCA with a fatal course that fails to respond to corticosteroids.

During GCA, strokes occur mostly in the vertebrobasilar territory (as opposed to atheromatosis-related CVA).

Given the frequency of strokes in elderly people, we must discuss the part concerning arteritis, steroids side effect and that of atheromatosis. A CVA can occur before the treatment begins but also at the beginning of treatment (median of 10 days) (Jouquan et al. 1984). The thrombosis-producing role of steroids in the genesis of these CVA has been reported in several retrospective series. The establishment of a steroid treatment could paradoxically favour the onset of cerebral infarcts in patients with intracerebral arteritis and does not prevent often fatal precocious ischemic relapses (Salvarani et al. 2009). This ischemic risk could be decreased by the association of aspirin at a low dosage (3 % against 13 %, p= 0.02) with steroids (Nesher et al. 2004; Lee et al. 2006; Robert et al.2006). But in the study of Berger et al. (2009) severe ischemic events occurred with high prevalence despite established platelet inhibition. Neither platelet count nor size was strongly associated with the risk of severe ischemic events (Berger et al. 2009).

When evaluating patients with dementia, it is common to check for easily reversible problems. Both clinicians and researchers should give more attention to looking for GCA as a routine part of the standard dementia workup. Mental status changes may be a prominent manifestation of GCA and precede and/or overshadow more classic signs and symptoms. Depression, agitation, confusion, and focal intellectual impairment have all been described (Alisky 2008).

For example, Morris and Lockie reported in 2005 a 76-year-old man with acute right-sided periocular pain and diminished vision. He had a sedimentation rate of 73 mm/hr, cilioretinal artery occlusion and “florid” GCA seen on temporal artery biopsy. He was quite impaired cognitively, but prednisolone 50 mg per day produced rapid normalisation of his mental status, and at that point, his family commented that he had actually had dementia for at least a few years. Further investigation revealed that three years before, he had suffered a right-sided middle cerebral artery stroke that had been accompanied by scalp tenderness and right-sided headache. A diagnosis of GCA had been considered at that time but was not pursued because sedimentation rate was only 4 mm/hr.

Peripheral neurological manifestations can be a mode of revelation of GCA but are considered as rare (Reich et al. 1990, Büschges et al. 1984). However, in the series where neurological involvement was systemically looked for, the frequency of peripheral neuropathies was estimated up to 14 %. In the majority of these cases, it is a sensory-motor polyneuropathy which is usually moderate and chronic, a mononeuritis or multineuritis. Radicular involvement, which essentially affects the cervical region, is much rarer. Isolated plexus brachial syndromes in the scope of multineuritis remain exceptional: no cases in the series of 260 GCA by Becourt-Verlomme et al. (2001); one case in 209 proven GCA in the series by Blaise et al. (2005). A review of the literature found around twenty observations of GCA with histological proof, complicated by a plexus brachial syndrome or low cervical radiculopathies on which we wish to focus (Blaise et al. 2005; Soubrier et al. 2002). The involvement is often inaugural and quite constantly involves root C5. There is a male predominance (54 %) of this complication as opposed to the female predilection for temporal arteritis. The unilateral or bilateral involvement with no predominant side occurs usually at the peak of GCA signs. It sometimes precedes the cephalic signs of GCA by a few weeks. Despite the frequent severity of the motor deficit, recuperation is the rule. The usually sudden character of the involvement suggests an ischemic mechanism and the cervical radiculopathies can be due to a florid giant cell arteritis of the lower radicular arteries. Whether ischemic or inflammatory, however, the mechanism of C5–C6 plexopathy is pure speculation.

9. Ophtalmological manifestations

The incidence of ophthalmological manifestations varies according to studies between 14 % and 70 % of cases. In 1998, Hayreh et al. (1998) reported a series of 85 patients suffering from GCA for whom opthalmological involvement was listed: amaurosis fugax 30.5%, loss of visual acuity 97.6%, diplopia 5.9% and ocular pain 8.2%. Therefore, GCA must be suspected in the case of a sudden loss of visual acuity, whether transitory or not, in a patient over 50. This loss of visual acuity might be linked to an acute anterior ischemic optical neuropathy 81.2% according to Hayreh et al. (1998) or, more rarely, central retinal artery occlusion 14.1%, isolated cilioretinal artery occlusion 14.1% and posterior ischemic optic neuropathy in 7%.
The risk of bilateral ocular involvement is major in the case of GCA. It still occurs in around 1 case in 4, even though it is avoidable in most of these cases. In the series by Maalouly et al. (2010), the average time lapse for a bilateralisation of ocular involvement was 17 days (0 to 210 days). This was a bilateral ischemic optical neuropathy: anterior 21 times and posterior twice, a bilateral retinal central artery occlusion 3 times, an ischemic optical neuropathy associated with transitory monocular blindness in the last case. No studied clinical or biological parameters were associated with bilateral ocular involvement risks. Ocular involvement was inaugural in 5 patients (no general signs). Bilateralisation occurred before any steroid treatment 15 times (56 %), 7 times (26 %) at least 5 days after a high dosage steroid treatment and 6 times in a longer-term steroid treatment at variable doses.
Steroids have resulted in a large reduction of the incidence of its ophthalmological complications, whose frequency however remains high for two main reasons: delay in diagnosis and the existence of ophthalmological complications inaugural of the disease. Thus, physicians must be aware of ophthalmological complications of GCA as the severity of the disease can be improved by an earlier diagnosis and treatment.
Berger et al. (2009) have reported a series of 85 GCA patients (78 histologically proven) and investigated how platelet count and size and platelet inhibition with aspirin relate to ischemic complications. Jaw claudication, amaurosis fugax, blurred vision, ischemic stroke and permanent visual loss were classified as "ischemic events"; ischemic stroke and permanent visual loss were sub-grouped as "severe ischemic events". Of the 85 patients, 62 (73%) presented with ischemic events, 29/85 patients (34%) with severe ischemic events. At the time of diagnosis 22/85 patients (26%) were treated with ASA. In multivariate analysis, neither platelet count nor size or aspirin treatment were significantly associated with ischemic or severe ischemic events.

10. Genital involvement

Genital lesions are exceptional. They can affect the ovaries, the uterus and the tubes. They are often discovered by chance, as female patients do not present painful pelvic symptoms.

Thus, in a review of the literature, Ducroix et al. (1990) report 11 cases of isolated ovarian lesions or associated with a uterine or tube lesion. Clinical signs of rhizomelic pseudopolyarthritis were present in four female patients and headaches in two female patients. The differential diagnosis of ovarian lesions of GCA is classically periarteritis nodosa and Wegener's disease. These two diseases can have a gynaecological tropism but the histological aspect is different.

11. Musculoskeletal symptoms

Rhizomelic pseudopolyarthritis is the most frequent rheumatic manifestation of GCA. The frequency of rhizomelic pseudopolyarthritis in the course of certified GCA is on average 40 % (Masson 2010). Conversely, the sub-group of rhizomelic pseudopolyarthritis which does not have, at the time of diagnosis, signs suggesting the coexistence of a GCA would only appear to have a low risk of developing a GCA later: out of a series of 400 cases of rhizomelic pseudopolyarthritis, only four patients (1 %) developed secondarily a clinical GCA (Spiera 1990).

Another work on 230 patients with rhizomelic pseudopolyarthritis with no clinical signs of GCA showed that these biopsies of temporal arteries carried out on a sample of 68 randomly-selected patients were only positive in three cases (4.4 % of the patients) (Mykelust et al. 2003). This frequency of 4 % confirms that most rhizomelic pseudopolyarthritis with no clinical signs of GCA are actually « pure » rhizomelic pseudopolyarthritis. The other rheumatoid manifestations are less frequent. They may be polyarthritis, oligoarthritis or monoarthritis affecting the large joints, and specifically the knees. The interest of the study by Belcourt-Verlomme et al. (2010) is above all to highlight the existence of monoarthritis or oligoarthritis affecting the large joints preceding GCA (nine observations with arthritis affecting large joints,260 with positive temporal artery biopsy in seven patients , with a time lapse of up to 24 months and reacting well to non-steroid anti-inflammatory treatments. Chronic seronegative polyarthritis with a symptomatology comparable to rhumatoid arthritis was also described. In the study of Navaez et al. (2001), the records of 163 cases of rhizomelic pseudopolyarthritis or GCA diagnosed over a 15 year period in one area of Spain were reviewed for the presence and type of musculo-skeletal manifestations. Of 163 patients, 90 had isolated rhizomelic pseudopolyarthritis and 73 had GCA. Eighteen of the 90 patients (20%) with isolated rhizomelic pseudopolyarthritis developed distal peripheral arthritis either at diagnosis or during the course of the disease. When it occurred, synovitis was asymmetrical, transient, and not destructive. Other distal manifestations observed in these patients were carpal tunnel syndrome and distal extremity swelling with pitting oedema. In all cases these manifestations occurred in conjunction with active rhizomelic pseudopolyarthritis. As expected, rhizomelic pseudopolyarthritis was the most frequent musculoskeletal manifestation in patient with GCA, occurring in 56% of cases. On the contrary, only 11% of patients with GCA developed peripheral arthritis. An important finding was that peripheral arthritis in these patients appears to be linked only temporally to the presence of simultaneous rhizomelic pseudopolyarthritis and it is not observed in its absence. The spectrum of distal musculoskeletal manifestations of rhizomelic pseudopolyarthritis in this study is similar to that reported in other populations. By contrast, distal musculoskeletal symptoms are uncommon in GCA.

When the joint fluid was analyzed, it was not specific. The analyses published in the literature show that it is a moderately inflammatory liquid, with less than 3 000 elements, and no specificity.

12. Conclusion

Giant cell arteritis (GCA) is a primary large-vessel vasculitis predominantly seen in the elderly that preferentially involves the external carotid artery and its branches. However, inflammation of the aorta and its branches, pericarditis, myocarditis, respiratory manifestations, neurologic symptoms including, but not limited to, stroke and blindness, as well as musculoskeletal manifestations occur in a subset of patient at diagnosis or during the course of the disease.

Unfortunately, its uncommon findings are frequently overlooked and too often GCA is considered a disease of the temporal arteries only. Awareness of the basic anatomy and pathophysiology of this disease will enable clinicians to recognize many more obscure presentations and provide treatment to prevent serious sequelae.

Extracranial involvement has probably been underestimated and its incidence may be more frequent than suspected. Systematic evaluation of patients with imaging techniques such positron emission tomography (PET) may reveal that the clinical impact of extracranial involvement by GCA may be more relevant than previously thought. In the setting of GCA an early diagnosis is mandatory in order to perform a treatment capable of avoiding the chronic and acute complications associated with an elevated mortality.

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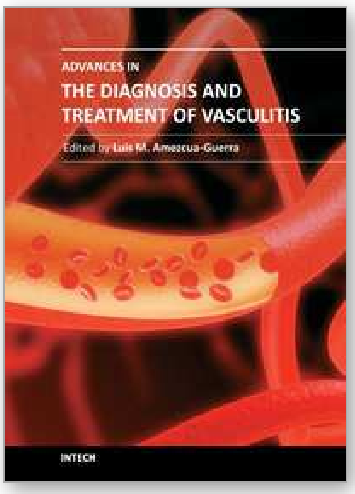

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This book represents the culmination of the efforts of a group of outstanding experts in vasculitis from all over the world, who have endeavored to draw themselves into this volume by keeping both the text and the accompanying figures and tables lucid and memorable. The book provides practical information about the screening approach to vasculitis by laboratory analysis, histopathology and advanced image techniques, current standard treatment along with new and more specific interventions including biologic agents, reparative surgery and experimental therapies, as well as miscellaneous issues such as the extra temporal manifestations of "temporal arteritis" or the diffuse alveolar hemorrhage syndrome. The editor and each of the authors invite you to share this journey by one of the most exciting fields of the medicine, the world of Vasculitis.