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The relevance of additional examinations requested during the diagnosis of retroperitoneal fibrosis - about a single-center study.

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I. Introduction:

Retroperitoneal fibrosis (RPF) is a rare disease characterized by fibrous and inflammatory sheathing of the main structures of the retroperitoneum [1]. Thus, it can envelop all the retroperitoneal organs and particularly the ureters leading to renal failure [2]. This entity comprises an idiopathic form (75% of the cases) and a group of "secondary" forms (25%) that are related to malignancies, infections, drugs, radiotherapy and other conditions [3]. In the absence of recommendations, the diagnostic approach remains essentially empirical. This approach may vary from one department to another, depending on the specialties concerned (internal medicine, nephrology, urology, etc.), the revealing symptoms or the habits of the teams [4].The aim of our monocentric study is on the one hand, to specify the main clinical and paraclinical characteristics and the therapeutic methods proposed for patients with FRP and, on the other hand, to analyze the diagnostic approach and the profitability of complementary examinations initially prescribed during the diagnosis.

II. Patients and methods:

We retrospectively collected 15 cases of retroperitoneal fibrosis hospitalized and followed up between January 2012 and January 2022 at the internal medicine and onco-hematology department at the UHC Hassan II in Fez .In the absence of consensual diagnostic criteria in the literature, the positive diagnosis of RPF was therefore retained either on the basis of a histological analysis from a biopsy fragment or in the lack of histological proof, by placing evidence on a CT scan of an infiltrate or "sleeve" regular and homogeneous tissue density, perivascular topography, sheathing the abdominal aorta more or less extended to the iliac vessels and can take contrast after injection. When a histological sample was taken, the diagnosis was retained in the presence of polymorphic fibro-inflammatory tissue composed of an infiltrate more or less dense in lymphoid, plasmacytoid, macrophage and eosinophilic polynuclear cells [5]. Given the retrospective nature of the study, the type of additional examinations carried out as part of the etiological assessment was not guided by any recommendation. Data collection was based on a pre-established grid of clinical, paraclinical and evolutionary data. This included data relating to routine biological examinations: complete blood count, sedimentation rate, CRP, serum creatinine, uremia, lactated dehydrogenase (LDH), serum protein electrophoresis, serologies and, when these were available, the results of more "targeted": antinuclear antibodies (ANA), polymorphonuclear anticytoplasmic antibodies (ANCA), and serum IgG4 assay.

III. Results:

They were nine women and six men. The average age at diagnosis was 48.4 ± 13.6 years with extremes ranging from 29 to 69 years. The average time between the first symptoms and the diagnosis was 330 days (between 1 month and 48 months). The reason for consultation was very variable, dominated by abdominal pain often associated with lumbar pain in 13 patients; general signs were reported by 10 patients, and dysuria by 2 patients. None of the patients showed signs of arterial or venous compression. The clinical examination had objectified in all our patients a sensitivity of the flanks or the lumbar fossae. Whereas the edemas of the two lower limbs were objectified in a single patient, and there were no clinical signs in favor of a sysmetic disease (table 1).

The diagnosis of the disease was made on the imaging data (abdominal CT scan in 8 cases, uroscanner in 6 cases, and abdominal MRI in one case) which showed panaortic fibrosis in 1 case and it was limited to the

circumference of the abdominal aorta in 14 cases. Nine patients presented a sheathing of the ureters and uretero-hydronephrosis with a destroyed kidney in one patient. The inferior vena cava was sheathed in four patients. Given the non-accessibility of positron emission tomography coupled to CT (PET-CT); the latter was not carried out at the time of the initial evaluation in only 02 patients, while five patients benefited from a re-evaluation by PET-CT during the follow-up (Table 2). Histology confirmed the diagnosis of FRP in 4 cases, highlighting inflammatory and histiocytic remodeling in 3 patients and dense connective tissue fibrosis without any signs of malignancy in a single patient. The biological explorations had shown renal insufficiency in 12 patients (80%) with an average serum creatinine of 68.41 mg/l (19-160 mg/l) and the presence of a biological inflammatory syndrome in 11 patients, i.e. 73.33%. While serum protein electrophoresis did not show any associated monoclonal gammopathy. Regarding the search for anti-nuclear antibodies, it was carried out in 12 patients without any diagnostic contribution. Measurement of the serum IgG4 level revealed a high IgG4 level in 3 patients (The value of IgG4 is greater than 1.35 mg/mL). And for the search for AFB in the sputum was negative in all cases. , while only one patient had active hepatitis C (the search for serum anti-HCV antibodies by the ELISA enzyme immunoassay test was positive) (Table 3).

Etiologically, four patients had secondary retroperitoneal fibrosis (secondary to IgG4 disease in 3 patients, to inflamatory aortitis in a single patient and of infectious origin in a single patient) while the idiopathic form was the most frequent in 10 patients or 66.6%. Of the 15 patients, 13 were treated with corticosteroids, and due to corticosteroid dependence or relapses, second-line treatment was offered in 4 patients (26%) including rituximab (n = 2), tamoxifen (n = 1), methotrexate (n = 1). Twelve patients underwent urinary drainage by double J ureteral catheter and no patient was put on emergency dialysis. The average duration of follow-up is 42.8 months (range 3-125 months) and under treatment; the evolution is marked by the disappearance of the pain, the improvement of the inflammatory syndrome and the normalization of the renal function in all the patients. Radiological stabilization is noted in 09 patients, two patients had a decrease in the mass, while two patients are not yet evaluated radiologically, only one patient had a complete disappearance of this mass and another was no longer visible.

IV. Discussion:

The purpose of our single-center retrospective study, in addition to the description of the clinicobiological characteristics of the patients is to evaluate the profitability of the additional examinations prescribed and to analyze our diagnostic approach. The number of patients included (N=15) is considered to be a small sample compared to that of the large series reported in recent years [4,6]. This could be explained by the multicentric nature of the latter. Our population was globally comparable to that of the literature, namely that the average age at the time of diagnosis is between 40 and 60 years old, with in 2/3 of cases a diagnosis of primitive or "idiopathic" FRP [3, 4 ,6]. On the other hand, the female sex was predominant in our series with a sex-ratio F/M of 1.5 contrary to several studies where there was a male predominance which is attributed to the higher incidence of aortic atherosclerotic disease in men at from the age of 40 [1, 2,7]. The revealing initial clinical signs were not very specific with in the foreground abdominal pain or lumbar pits, which are estimated to be present in 90% of patients [2,5,8]. Therefore, as a general rule, the initial clinical presentation does not make it possible to differentiate the primary RPF from the secondary form but, should push the practitioner to continue the investigations. In our series, the biological markers of inflammation (VS, CRP) are elevated in two-thirds of cases, as described in the literature [1]. These biological tests are often used to monitor clinical progress, although they do not always reflect disease activity [1]. Whereas for serum protein electrophoresis, the main interest was the search for an associated monoclonal gammopathy, which is something not labeled in our population. In view of our retrospective analysis, the search for autoimmune markers was non-contributory and no diagnosis of an autoimmune disease was retained, and these results were also reported in a French multicenter study which evaluated the relevance of additional tests carried out for diagnostic purposes, in particular ANA and the dosage of tumor markers [4]. Concerning the serum IgG4 dosage, its purpose is to detect the hyper-IgG4 syndrome or multiple IgG4 fibrosclerotic disease which is an entity of recent description (2002), characterized by "storiform" fibrosis [1], whose diagnosis is based on criteria: 1) clinical: swelling or mass located on one or several organs; 2) biological: elevation of the serum level of IgG4 greater than 1.35 g/L; and 3) histological: marked infiltration by lymphocytes and plasma cells, with plasma cells expressing IgG4 greater than 10 per field with an IgG4/IgG N ratio of 40%. The diagnosis is certain if the 3 criteria are present, probable if criteria 1 and 3 are present, and possible if criteria 1 and 2 are present [9]. In our series, given the recent description of the "disease associated with IgG4", the immunohistochemical analysis did not include labeling with an anti-IgG4, and the IgG4 assay was performed in just 6 patients, returning positive in three patients. Our results are consistent with several series of idiopathic RPF (iRPF) which assessed the proportion of patients meeting the criteria for IgG4-associated disease and whose serum IgG4 levels are increased in 20-40% of FRP cases. These series concluded that it is unclear whether the IgG4-related forms of RPF are a separate entity from FRPi, or whether they are the same disease at different stages and/or with different clinical

expressions. [9]. Knowing that on the therapeutic level, there is to date no data suggesting that the demonstration of an FRP in the context of a hyper IgG4 syndrome modifies in any way the initial therapeutic management and follow-up [4]. However, it is imperative for new prospective studies to clearly differentiate these two terms in order to clarify the prognosis and the response to treatment. Taking into consideration the inclusion criteria, abdominal CT and renal magnetic resonance imaging (MRI) were the reference examinations to diagnosis RPF. These two examinations occupy not only a central place in the diagnosis, but they also make it possible to suspect a secondary RPF when it is about an atypical extension (above the renal artery or at the thoracic level) and differentiate an RPF from an atheroma or an aortic aneurysm, as demonstrated in the French multicenter study [4] and the Dutch series [10]. On the other hand in our series, there was no correlation between imaging findings and RPF type. In other words, the imaging did not allow us to single out the idiopathic RPF, which will allow the practitioner to reduce the para-clinical examinations for diagnostic purposes. The most recent use of PET-CT has the advantage of offering a global assessment of the body and allowing the detection of tumoral processes or multifocal damage (disease associated with IgG4), but its main interest remains the reassessment of the disease and the prediction of relapses [9]. In other words, PET-CT is the reference examination for monitoring RPF.

Regarding the need for histological confirmation in front of a chart strongly suggestive of RPF on imaging, in our series; 26% of the patients had a biopsy for diagnostic purposes which showed non-specific fibro-inflammatory tissue without any criterion of malignancy or signs pointing to the secondary form. At the end of these data, it therefore does not seem to us legitimate to perform a biopsy systematically when the appearance and topography of the RPF are typical on the scanner and there is no other clinical or radiological call point on imaging; and this was also proposed by the French study [4]. On the other hand, biopsy is strongly recommended in cases where the RPF shows signs of malignancy on imaging or in the event of corticosteroid resistance [11].

V. Conclusion

Despite the monocentric nature of our study, it suggests that in the absence of clinical or paraclinical guidance, the performance of certain non-invasive examinations (ANCA, anti-nuclear AC, tumor markers) does not seem relevant. Similarly, the "systematic" performance of an RPF biopsy does not seem justified in the presence of a typical RPF appearance and topography on conventional imaging data (CT or MRI). On the other hand, in our study, these radiological examinations have no profitability with regard to the differentiation between idiopathic and secondary RPF, which should have limited certain paraclinical examinations.

Initial clinical manifestations	n (%)
Asthenia	10(66.6)
Fever	10(66.6)
Pain (abdominal or flank or lumbar)	08(53.3)
Dysuria, oliguria	02(13.3)
Asymptomatic patient	1(6.6)

Table 1: Initial clinical manifestations

Patient (n=15)	Abdominal scanner or uro-scanner	PET SCANNER
Patient N : 1	Aspect of retro peritoneal fibrous matrix which surrounds the abdominal aorta under renal. Bilateral hydronephrosis uretero predominant on the right side.	
Patient N : 2	Retroperitoneal infiltration encompassing the aorta and the inferior vena cava, dilatation of the bilateral renal pyelocalicielles cavities	
Patient N : 3	Presence of retroperitoneal fibrosis with difficulty in distinguishing the fibrosis of the vessels	The hypermetabolic character of known retroperitoneal fibrosis without associated suspicious hypermetabolic focus. Intense hypermetabolism of the aortic wall more marked at the level of the ascending aorta, the arch and the subrenal aorta compatible with aortitis
Patient N:4	Retro peritoneal tissue mass (9.3 * 3.3 cm) compatible with lymph node casting responsible for bilateral ureterohydronephrosis	
Patient N : 5	Appearance most likely in favor of retroperitoneal fibrosis, responsible for moderate bilateral ureterohydronephrosis	
Patient N : 6	Presence of a large retroperitoneal lymph node cast encompassing the aorta as well as the vena cava extended over approximately 11 cm x 4.7 cm which is responsible for the left ureterohydronephrosis	Presence of a retroperitoneal tissue mass encompassing the large vessels without associated hypermetabolism, SUVmax at(2.1).
Patient N : 7	Dilatation of the moderate bilateral renal pyelocalicielles cavities, presence of a retropiroteneal tissue flow in contact with the large vessels	
Patient N :8	Appearance of primary or secondary retroperitoneal fibrosis responsible for bilateral dilatation of the pyelocalicielles cavities more marked on the left.	Hypermetabolic character of the retro-peritoneal fibrosis extended in height from the renal pedicle to the primitive iliac pedicles in favor of its active character.
Patient N :9	Tissue infiltration of the retroperitoneal related to retroperitoneal fibrosis. Absence of uretero hydronephrosis.	
Patient N :10	Presence of a retroperitoneal mass localized on the right measuring 6 cm * 5 cm * 15 cm, which enhances weakly, having in contact with the aorta with a border of separation, and in contact with the psoas and the left renal artery	Moderately hypermetabolic prevertebral retroperitoneal lesional process encompassing the large vessels and the right ureter.
Patient N :11	Mass encompassing the aorta in its sub-renal portion measuring 5.8 cm transversely x 5 cm in height compatible with retroperitoneal fibrosis which is responsible for bilateral uretero-hydronephrosis	Metabolically inactive retroperitoneal fibrosis -Absence of other sites of fibrosis
Patient N :12	Appearance in favor of a retroperitoneal tissue infiltrate encompassing the inferior vena cava, the aorta under the kidney, and coming into contact with the 02 lumbar ureters with bilateral ureteropyelic ectasia, in favor of retroperitoneal fibrosis first.	
Patient N :13	Periaortic tissue infiltration under the renal arteries sheathing the abdominal aorta at L4, as well as the primitive iliac arteries, without dilation of the excretory cavities upstream.	Fibrosis or magma of adenopathies at the retro-peritoneal level, discreetly hypermetabolic (SUV = 2.7) (the most hypermetabolic focus (SUV = 3.1) is in the interaortico-caval extending to the bilateral iliac level (SUV = 2.2)
Patient N :14	Moderate right pyelocaliciel dilation, periaortic tissue infiltrate, related to retroperitoneal fibrosis.	Retroperitoneal fibrosis, described morphologically, is not hypermetabolic.
Patient N :15	Tissue infiltration encompassing the aortic-caval and iliac axis, extends to the right renal pedicle and perirenal fat, measuring approximately the largest 69 x 37 mm in diameter.	

Table 2 : The imaging characteristics of patients with RPF

Biological examinations	n (%)
Increase in CRP or VS	11(73.3%)
Renal failure	12(80%)
Anemia (<12g/dl)	3(20%)
The value of IgG4 (n=6)	2(13.3%)
Search for AAN (n=12)	0(0%)

Table 3: Characteristics of additional biological examinations performed in patients with RPF

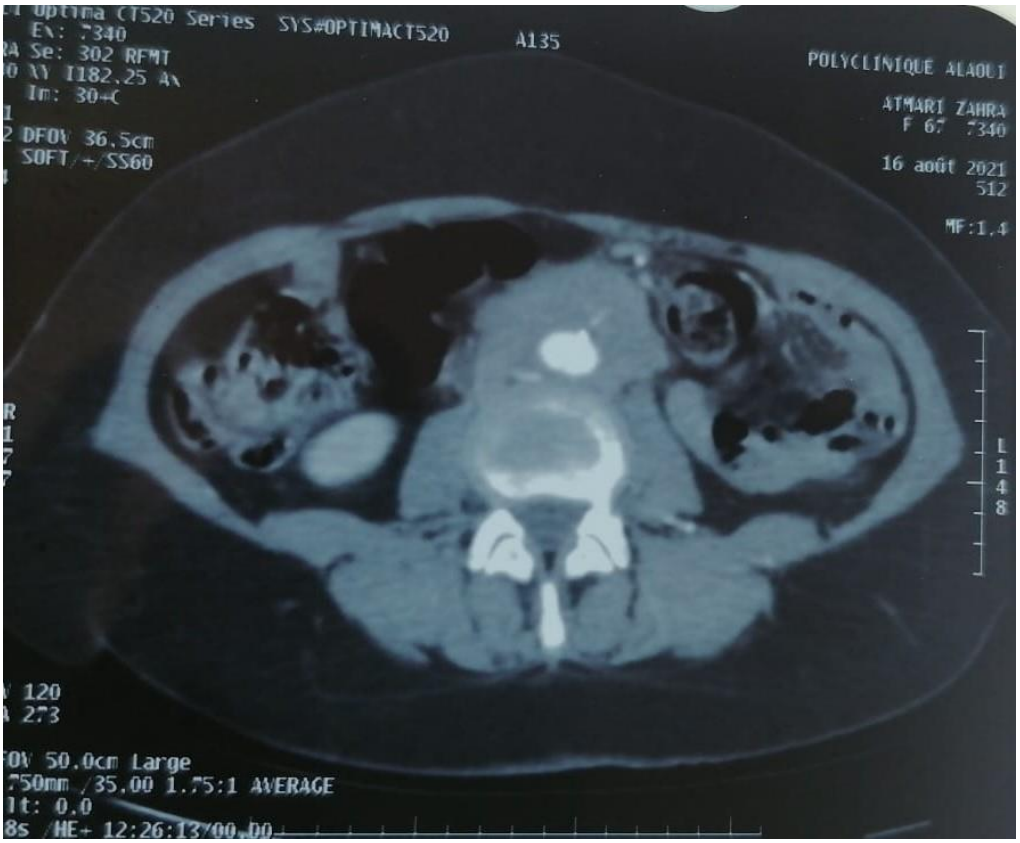

Figure 1: CT appearance of retroperitoneal fibrosis showing a periaortic tissue mass with a density comparable to that of muscles.

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