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A sarcoïdoses inducted by an anti-TNF alpha revealed by a renal failure

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Abstract

Sarcoïdosis is a systemic granulomatosis of unknown causes. The pathophysiology involves many protein of the inflammatory response like the TNF alpha, who's playing a major role in the development and persistence of the disease. The development of a sarcoïdosis in patient under anti-TNF alpha is uncommon, integrating a paradoxical effect of class. In this context, the sign of the disease is not always pulmonary. Our aim was to present a case of a sarcoïdosis induct by an anti-TNF alpha revealed by a renal failure, in a 79 old man under ETANERCET for a psoriatic arthritis. After 37 month of treatment he present a rapid progression of the renal failure over 6 month with a hypercalcemia. The renal biopsie showed a granulomatosis nephritis without caseous necrosis. The diagnosis of a sarcoïdosis was evoke. The responsibility of the ETANERCEPT where retain before the absent of other aetiology found and his know relationship with the development of granulomatosis. At this argument added, the good evolution of the patient after the stop of the medication associated with a digressive dose of glucocorticoid in 7 month. A sarcoïdosis induced by anti TNF alpha is rare, as well as his revelation by renal failure. Our observation remind this two possibilities, and the necessity of a thorough follow up of patients under biotherapy.

Keywords

Anti-TNF-alpha; renal failure; chronic arthritis; sarcoïdosis; paradoxical effect of class.

Abbreviations

ARF: Acute renal failure; CIR: Chronic inflammatory rheumatism; HSV: Human simplex virus; INF: Interferon; MTX: Methorexatr; PTH: Parathyroid hormone; TNF: Tumor necrosis factor.

Introduction

Sarcoïdosis or Besnier-Boeck-Schaumann disease is a systemic granulomatosis of undeterminated cause. The development of this disease is complex and involves pro-inflammatory cytokines including the TNF-alpha. Its incidence in the patient under anti-TNF alpha is rare, especially reported from patients with chronic inflammatory rheumatism [1]. The extra-throracic manifestations are rarely isolated. Kidney damage is encountered in less than 10% of cases and rarely leads to renal failure (<1%). They are most often related to acute renal failure due to hypovolemia on acute hypercalcemia, or a chronic nephrocalcinosis leading lithiasis. The tubulo-interstitial sarcoïdosis nephropathy is less common, while glomerulopathies are very rare [2]. We report a new observation of sarcoidosis granulomatosis in a patient under ETANERCEPT for seronegative Chronic Inflammatory Rheumatism (CIR) revealed by renal failure.

Case Presentation

Mister M 79 years old without particular renal antecedent, followed for psoriatic rheumatism for 4 years (june 2015) was treated in first intention by METHOTREXATE 20 mg (MTX) injection during 6 month which was stopped due to peneumopathy infectious. A weekly subcutaneous injection of ETANERCEPT (ENBREL 50 mg) was introduced, with a clinico-biological follow up every 3 month. The treatment was well tolerated and a complete remission was noticed after 24 months of treatment (January 2018). At the 37 months of treatment (February 2019), a slight rise in creatinine to 101 µmol/L was noted and persist after a check out at the third month (138 µmol/l). Three months later, the patient was hospitalized in Rheumatology department of the Avignon Hospital Center for deterioration of general state with a chronic asthenia and a major loss of weight (6 kg in 4 month), these symptomatologies were associated with a Sadoul stage 2 of dyspnoea and a severe degradation in renal function (247 µmol/l of creatine).

At the admission, the Corporal index Mass of the patient was calculated to 24, 74 kg/m^2, he was apyretic with normal oxygen saturation. The pulmonary auscultation revealed a crackling rales predominating at both pulmonary basis. The rest of examination was normal. The biological test showed a severe renal insufficiency with a creatinine level at 239 µmol/l and an azotemia of 12 mmol/l. The blood ionogram, the hepatic and martial test were normal. There was no biological inflammatory syndrome. The haemogram showed a normochromic normocytic anemia (115 g/dl) without abnormalities in vit b12 rate nor plasma folate level. The reticulocytes and other blood lines were normal. Concerning the phosphocalcic test, we found a corrected hypercalcemia at 3, 32 mmol/L, phosphoremia and bone alkalines phosphatases was normal. The Parathormone (PTH) was adapted to the hypercalcemia (13 pg/l), in the absence of PTH rp. The plasmatic (1,25) OH vitamin D3 rate was increased to 113 µg/L. A serum protein immunoelectrophoresis was requested and had objectified a monoclonal fraction of the gammaglobuline (IgG kappa type 8, 8 gL). The absence of typical lacunar bone lesions on skull, pelvis and long bone radiography as well as the negativation of the proteinuria with the rare 3% plasma cell infiltration in the myelogram permit to exclude the diagnosis of myeloma. The uricemia was increased to 482 µmol/l. The urinary test revealed a calciuria at 12,4 mmol/24h without another abormalities. The renal ultrasound doesn't show any lithiasis nor hydronephrosis image but a normal renal size. The PSA rate was normal (0, 92 ng/l).

The hypothesis of granulomatisis was finally retained in front of hypercalcemia with adapted PTH and elevation of plasma (1, 25)OH D3 vitamin. The plasma angiotensin converting enzyme essay to 150 µg/l pleaded for this diagnosis. The autoimmune and the infectious test were negative. The C4 complement was not consumed.

The thoracic CT scan had revealed multiples adenopathies of the mediastinal lobes especially subcarenal and bilateral hilar area, an alveolar condensations syndrome and interstitial syndrome in the 2 lower lobes (Figure 1). Any tumoral lesions were detected in the abdomino-pelvic stage.

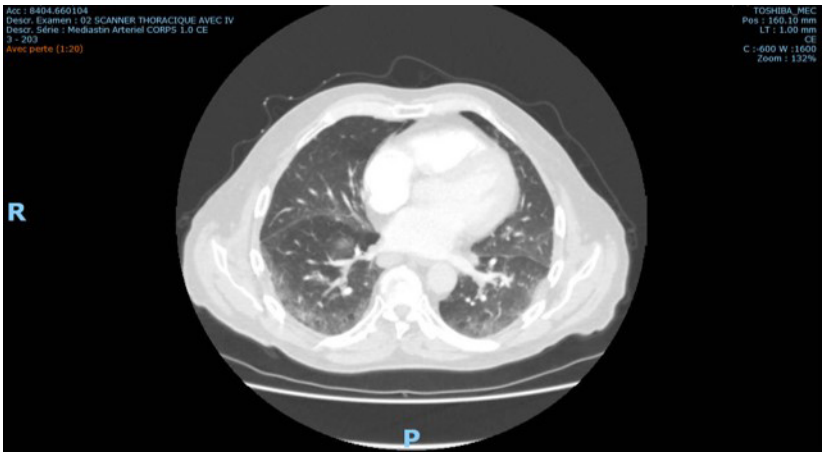

Figure 1: Thoracic scan ,axial section, parenchymal and mediastinal window: Multiple adenopathies of the mediastinal lobes, especially bilateral subcarenal and hilar as well as alveolar condensations and an interstitial syndrome in the 2 inferior lobes

A bronchial fibroscopy showed a normal macroscopic aspect, the broncho-alveolar liquid (BAL) has a hypercellularity with lymphocytary predominance (70%). The BAL was free of acid-fast bacilli, cytomegalovirus, HSV1, HSV2, enterovirs and rhinovirus after assessment. The biopsy of the bronchus mucosae remains normal. Accessory salivary glands biopsy was at the limit of normal. The left renal biopsy was performed in view of the absence of improvement in calcemia and creatinine level despite of the adequate hydratation and ZOLEDRONATE therapy. It revealed a granulomatosis interstitial nephritis without central caseous necrosis, suggesting the diagnosis of sarcoïdosis with renal involvement. At the glomerular level: A glomerulus showed a fibrosis involution in sealing bread some rare floculo-capsular junctions were noted, and the absence of cell proliferation especially in the mesangial area. At the tubule-interstitial level: a moderate multifocal interstitial fibrosis with a heterogeneous repartitions was found. It co-existed with a polymorphic inflammation with giant cells micro-granulomas aspect. Concerning the tubes: an aspect of suffering epithelial was presented without calcium-type precipitation. At the vascular level, the arteries showed a sub-intimal fibrosis with a discrete reduction of the vascular lumen, without vasculitis aspect (Figure 2 & 3). It should be noted that the immunofluoerescence showed discrete mesiangium IgA deposits. The absence of clinical history of haematuria and his age ruled out the diagnosis of Berger's disease.

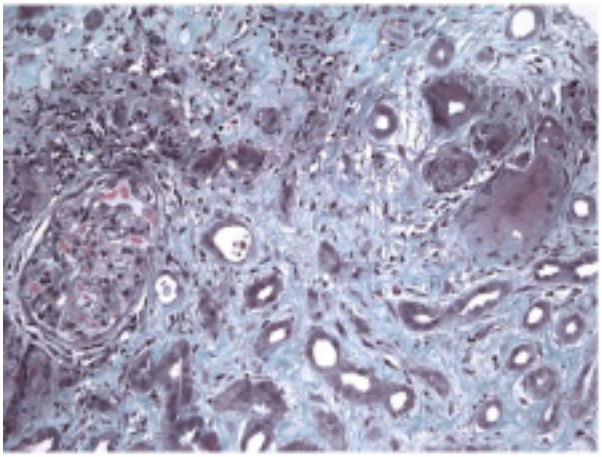

Figure 2: (Masson's trichrome x 200)

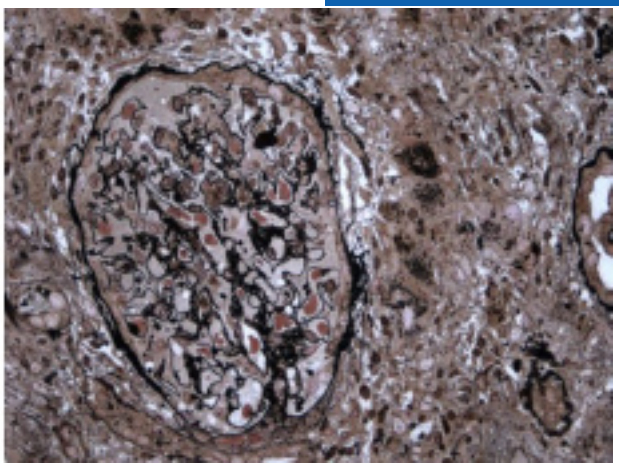

Figure 3: (jones: x400): histological image ,on light microscopy: Intersticial nephritis with giant cell lesions, without caseous necrosis and in absence of any sign of vasculitis

At the end, the diagnosis of a systemic sacroïdosis granulomatosis like induced by ETANERCEPT was retained, with pulmonary, mediastinal and renal manifestations, in a patient treated for a psoriatic rheumatism for 4 years. The research of other possible localizations of sarcoïdosis was negative. Thus, ETANERCEPT was stopped and a corticosteroid therapy per os (1 mg/kg) for 2 months followed by a progressive decrease. The evolution was favourable, the renal function was progressively recovered with diminution of calcemia rate and plasma (1,25) OH vitamin D. The corticosteroid was stopped at the 7th month of treatment and the renal function remains normal (GFD to 65 ml/mn), the calcemia and the vitamin D3 remains also normal.

Discussion

Sarcoïdosis is a multifactorial systemic granulomatosis. Its etiopathogeny is poorly understood but would probably involve an uncontrolled inflammatory reaction to antigen stimulation of unknown origin. This stimulation will cause the activation of the inflammatory cells (macrophages, T lymphocyte) whose chronic activation leads to the formation of an epitheloid and gicantocellular granuloma without caseous necrosis typical of the disease. This reaction is accompanied by increased production of inflammatory cytokines (IL-2, IL-12, IL-18, IL27, IFNc, and TNF alfa) [3]. The apparition of sacroïdosis in a patient under TNF alpha is part of paradoxical effect in this biotherapy class in the same way as psoriasis (de novo or aggravated) [4]. This paradoxical effect is mainly reported for the patient with chronic inflammatory rheumatism and would be the result of direct and indirect effect of the medication. Our observation reported a case of sarcoidosis under ETANERCEPT which was revealed as renal failure.

The renal impairment of sarcoidosis occurs in less than 10% of patients. The renal failure is much rarer (<1%), and may either be indicative of the progression or the exposure of the disease [5]. It can have 3 mechanisms: abnormal phosphocalcic metabolism, tubulo-interstitial involvement and glomerulopathie.

The common renal damage is related to phospohocalcic metabolism disorders. Hypercalcemia is encounterd in 10 to 15% of patients with sarcoidosis and hypercalciuria is observed three times more

frequently. These metabolic disorders are due to the hydroxylation of vitamin D by the macrophages of the sarcoid granuloma. They can be responsible of the diminution of the glomerular filtration and tubular function or more rarely neprhocalcinosis (3 to 5%) or urinary tract lithiasis with obstructive renal failure (10%) [6]. The diagnosis of nephrocalcinose is suggested by the calcifications of the renal parenchyma visualized on the ultrasound or the abdominal CT scan without injection. It can be confirmed by calcium deposit in the renal histology. The obstructive renal lithiasis failure is evoked by the renal US. The specific treatment of hypercalcemia or hypercalcemic renal failure in sarcoidosis is a systemic corticosteroid therapy at low doses (0,3_0,5 mg/kg/day). The prognosis is generally good in the majority of cases [7].

The tubulo-interstitial involvement is reported in about sixty cases in the literature, much less common than the anterior mechanism. It seems to have a masculine predominance with peaks in frequency between the 3rd and the 6th decades of life. The clinical presentation is an Acute Renal Failure (ARF) without extra renal signs, which makes diagnosis difficult. Otherwise, the extra renal localization precedes the renal involvement by 4 month to 9 years, and the renal failure then occurs in a context of multivisceral disease [8]. In all cases, ARF is rapidly progressive. In our case, a 79 years old man who had been on ETANERCEPT for 43 months, and presenting an acute renal failure of rapid progression. The histological study can reveal either lymphocyte and interstitial macrophage infiltrates or sarcoïdosic granuloma, with intacts glomeruli and vessels in both cases [9]. However, renal sarcoidosic granulomas prevalence was 7 to 30 % of cases in autopsy series of patient with sarcoidosis [8,10]. The biological elements in favour of the diagnosis were not very specific, they are mainly abnormality of urinary sediments (abacterial leukocyturia, proteinuria, hematuria). In routine practice, the renal workup should include creatinine, calcemia, 24-hours calciuria and CBEU (cytobacteriological examination of the urine) The association of renal failure with normal rate of calcemia lead to a renal biopsy. The treatment of tubulo-interstitial nephropathy requires corticosteroid therapy (1 mg/kg/d) within 2 month followed by a decrease over a minimum of 12 months. The initial evolution is usually favourable except in cases of delayed treatment where chronic renal failure is common. The rebounds effect were common mainly under 8 mg/d of prednisone [11].

The third, much rarer mechanism is glomerular nephropathy. The extra membranous glomerulonephritis is the most commonly described. This type of lesions is much rarer, the prognosis is variable and the treatment is not standardized [12].

In our observation the ARF is hypercalcemic with vitamin D3 deficiency, the PTH was adapted. The plasma ACE elevation was in favour. The anomaly of the urinary test was mostly hypercalciuria without calcium microcrystals. The ultrasonography of the urinary tract eliminated obstructive cause. The histologic diagnosis was predominantly in favour of a sarcoidosis tubulo-interstitial granulomatosis nephropathy. The evolution was favourable under corticosteroid therapy with a complete remission at the 7th month of treatment. Our case is similar to those described by Mac Curley [2] and Hannedouche [10]. They reported as well 3 cases of ARF due to a granulomatosis nephropathy without nephrocalcinose. However the discordance between relatively moderate hypercalcemia and the severity of the renal failure is striking. In Guenel's study [13] relating to 22 sarcoidosic interstitial nephropahies, granulomatosis nephropathy and nephropathy connected to calcic disorders is more often associated. In addition, hypercalemic ARF in sar-

coidosis is generally more severe than the one in hyperparathyroidism for example. This may be in favour of the presence of subclinical sarcoidosic renal lesions. Thus hypercalcemia is in certain circumstances, as here, the triggering factor for renal failure occurring in pre-existing granulomatosis nephropathy.

Concerning TNF alpha, it is a pro inflammatory cytokines secreted by activated macrophages. It has a major role in pathogenesis of chronic inflammatory disease, responsible for the recruitment of the type 1 Helper T cells in granulomatosis process [14]. The anti TNF alpha are considered as adjunctive therapy in various inflammatory diseases, are used in rheumatology in patients with rheumatoid arthritis, psoriatic rheumatism, ankylosing spondylitis. There are three types of anti TNF alpha: ETANERCEPT (ENBREL®), INFLIXIMAB (REMICADE®) and ADALIMUMAB (HUMIRA®). In our case, the patient was under ETANERCEPT, a fusion protein associating a soluble p75 TNF alpha receptor and the constant portion of human IgG1.

As all immunosuppressive drugs, the main side effects of anti TNF are infectious and must be monitored as there is a possibile reactivation of latent tuberculosis [15]. Besides this classic side effect, this type of medication can induce paradoxical effects. In fact,it is the appearance of pathology that is supposed to be treated by the anti TNF alpha agent itself [4,16]. In order to speak of paradoxical effect, the patient receiving the medication must have no clinical manifestation of the induced condition that must appear after a variable duration of exposure to the anti TNF alpha.

In our observation, the diagnosis of ETANERCEPT- induced sarcoidosis was posed. For intrinsic imputability, manifestations began to appear after 37 months of ETANERCEPT in a patient who had no antecedent of sarcoidosis. The hypercalcemia can occur in diverse pathological conditions. A primary hyperparathyroidism was rejected by the low rate of intact parathyroid hormone, suggesting the extra parathyroid origine of hypercalcemia. Investigations for multiple myeloma and other neoplasia returned negative. The patient had no new suspicious drugs introduced. No abnormalities in the autoimmune test and the search for infectious granulomatosis (including tuberculosis) were not found. The association of extra parathyroid hypercalcemia with an abnormal high level of 1-25 hydroxy-vit D and pulmonary interstitial syndrome led us to the diagnosis of granulomatosis. Indeed, pathological exploration of renal involvement was consistent with sarcoid granulomatosis. The evolution was favourable after the discontinuation of ETANERCEPT associated with corticosteroid therapy.

For the extrinsic imputability, the first documented case of an induced sarcodosis by anti TNF alpha was in 2002 [17]. The number of cases increased gradually with incidences reaching 0,04% in one year and 1,82% in 6 years [18], according to French and Australian statistics respectively. The clinical presentation is heterogeneous. Lungs (62%), lymphatic nods (59%), and skin (24%) are the most concerned [17]. The renal damage notably by ETANERCEPT as in our patient is very rare. The granulomatosis induced by anti TNF alpha agent is reversible or tends to improve after the interruption of the medication. Prednisone is prescribed in some cases like ours in response to a slow improvement in renal function after stopping ETANERCEPT. However the prognosis is good in the majority of cases with a complete remission [1,18].

Nevertheless, a fortuitous association remains possible, by the appearance of a sarcoidosis independently of anti TNF alpha treatment. In our case, the patient's age was one of the supporting criteria to

exclude this fortuitous association since a late start of a sarcoidosis is extremely rare [19].

The mechanism by which the anti TNF can induce a granulomatosis is not yet fully elucidated. One of theories is the presence of an elevated rate of IFN gamma an essential cytokine in the development of granuloma; in the patient undergoing TNF therapy (of any type). The risk is added for ETANERCEPT because of its pharmacological properties which are completely different from ADALIMUMAB and INFLIXIMAB. It significantly reduces the number of CD4 and CD8 T-lymphocytes secreting TNF alpha and IFN gamma. It inhibits completely the TNF alpha by partially binding the p-75 fraction of the TNF receptor. Finally, it improves the biodistributon of TNF alpha without blocking its bioactivity [20].

Conclusion

In a patient under anti TNF alpha, a regular follow up is necessary. Besides the common infectious complications, the sarcoidosis induced by this medication is rare but remains possible even with its renal failure manifestation. It must be evoked after elimination of other causes of granulomatosis especially tuberculosis, with rigorous imputability criteria. The prognosis is often good after discontinuation of the treatment associated with a corticosteroid therapy, justifying the early diagnosis necessity.

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