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Case Report

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A Rare Case of Cholangiocarcinoma Complicating C-Anca Vasculitis

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ABSTRACT

Antineutrophil cytoplasmic antibody (ANCA) - associated vasculitis is a severe autoimmune disorder. Its prognosis has been markedly improved by the introduction of immunosuppressive treatments. Nevertheless, this has been associated with an increased incidence of malignancy. We report the case of a 60-year-old woman who presented C-ANCA vasculitis with renal failure and pulmonary involvement requiring immunosuppressive therapy. A complete remission was achieved. After a follow-up of 22 months, she presented asthenia with fever and jaundice. The diagnosis of locally advanced peri-hilar cholangiocarcinoma was made. The outcome was unfavorable and the patient died. The incidence of malignancies is increased in ANCA vasculitis. Biliary tumors are uncommon compared to other cancers. The risk is mainly related to exposure to cyclophosphamide.

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Introduction

Antineutrophil cytoplasmic antibody (ANCA) -associated vasculitis are necrotizing vasculitis affecting small-caliber vessels grouping together granulomatosis with polyangiitis (GPA), microscopic polyangiitis and eosinophilic GPA [1]. The coexistence of vasculitis associated with ANCA and neoplastic disease is common. This association has been reported mainly with bladder tumors, skin tumors and hemopathies. Rarely, they can be seen in solid cancers, especially lung, colic and kidney [2]. Although the role of immunosuppressive therapy in the pathogenesis of these tumors has been established by several authors, other mechanisms that explain this relationship remain unclear. We report a particular case of cholangiocarcinoma occurring in a patient followed for ANCA vasculitis.

Case report

A 60-year-old woman with a medical history of hypothyroidism and ANCA -associated vasculitis consults for asthenia with fever. The diagnosis of vasculitis was made two years earlier. She was hospitalized for the management of severe renal failure with asthenia. Clinical examination revealed oligo-anuria with the presence of two-cross proteinuria and microscopic three-cross hematuria on the urine dipstick. Blood pressure was normal and pulmonary auscultation found crackling rales in the right pulmonary field. The biological assessment demonstrated rapidly progressive renal failure with an increase in serum creatinine from 256 µmol / l to 748 µmol / l in three days, associated with a biological inflammatory syndrome. The rest of the biological results are summarized in Table 1. The immunoassay found an elevated level of C-ANCA with anti-proteinase 3 (PR3) specificity. Anti-glomerular basement membrane antibodies were negative. The thoracic computed tomography showed right apical parenchymal condensation with an eccentric excavation and pulmonary embolism of the left basal artery. Analysis of the bronchoalveolar lavage fluid did not show evidence of intra-alveolar hemorrhage. The diagnosis of GPA-type ANCA vasculitis was made due to rapidly progressive glomerulonephritis, pulmonary involvement and the presence of serum C-ANCA directed against PR3. The renal biopsy was not performed due to the curative anticoagulation prescribed for the pulmonary embolism. The treatment also included corticosteroid therapy based on methylprednisolone at a dose of 1 g / d three days, relayed by prednisone at a dose of 1 mg / kg / d, associated with cyclophosphamide (500 mg / bolus, 3 boluses at 15 days interval and 3 boluses 21 days apart). The outcome was favorable with normalization of serum creatinine after 3 months. Maintenance therapy was a combination of corticosteroid therapy at a dose of

10 mg / day and mycophenolatemofetil at a dose of 1.5 g / day.

After 22 months of follow-up, the patient presented with an asthenia with generalized pruritus. She was hospitalized in a surgical intensive care unit. Clinical examination revealed fever at 38.8 ° C with jaundice and tenderness on palpation of the right hypochondrium. Laboratory findings showed predominantly conjugated hyperbiluribinaemia associated with hepatic cholestasis and cytolysis with a biological inflammatory syndrome. The laboratory results are summarized in Table 1. The assay of the tumor markers showed a high level of carbohydrate antigen (CA 19-9) (319 IU / l).

Table 1: Results of the biological test

Parameter	1st hospitalization	2nd hospitalization
Creatinine (µmol/l)	748	68
CRP (mg/l)	56	46
Sed Rate (mm/h)	116	70
White cells (/mm3)	11150	7480
Hemoglobin (g/dl)	8,1	12,5
Aspartate transaminase (UI/l)	19	129
Alanine transaminase (UI/l)	17	152
Total Bilirubine (µmol/)	4,1	380
Conjugated Bilirubin (µmol/l)	0,3	341
Alkaline phosphatase (UI/l)	47	307
Gamma-glutamyl transpeptidase (UI/l)	41	402

CRP : C-réactive protéine ; Sed Rate : sedimentation rate

Magnetic resonance imaging (MRI) showed dilation of the intrahepatic bile ducts upstream of a suspicious circumferential thickening of the biliary convergence suggesting a tumor origin (Figure 1). There was no metastasis. The patient had had external biliary drainage and then underwent surgery. Intraoperatively, it was a peri-hilar tumor invading the hepatic pedicle and duodenum with multiple suspect nodes. The tumor was considered unresectable. Histological analysis of the intraoperative biopsy concluded that a moderately differentiated adenocarcinoma, compatible with cholangiocarcinoma. The patient had started palliative chemotherapy. She died quickly in the post-operative course.

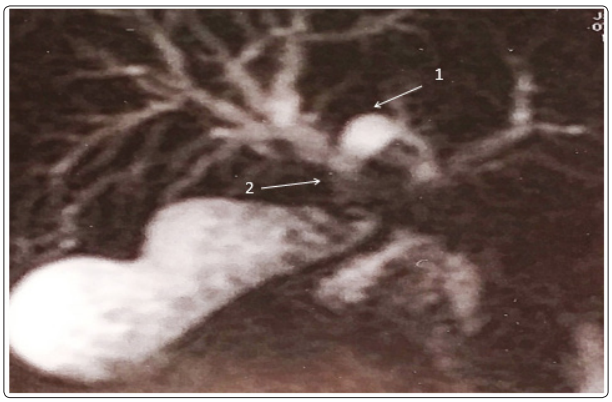

Figure 1: Appearance of peri-hilar cholangiocarcinoma on MRI: (1) dilation of the bile ducts; (2) tumor obstacle

Discussion

In the literature, several studies have shown a significant increase in the incidence of neoplastic disease in patients with ANCA vasculitis compared to the general population. The most frequent tumors are bladder tumors, skin tumors (excluding melanoma) and leukemia [2,3]. This risk appears to be greater in patients with C-ANCA / PR3 vasculitis compared to those with positive P-ANCA / MPO levels [3]. In contrast, the association of ANCA vasculitis and solid cancer is rare. In a recent meta-analysis, Shang et al. showed an increased risk of hepatic (odds ratio: 3.84) and pulmonary (odds ratio: 1.67) tumors in ANCA vasculitis [4].

Cholangiocarcinoma after 22 months of onset of illness. This association has been rarely described in the literature. A similar case has been reported in a clinical trial investigating the place of etanercept (an anti-TNF) in the treatment of GPA. This was a 60-year-old woman with GPA with kidney and lung involvement. Induction therapy combined conventional corticosteroid and cyclophosphamide therapy with etanercept. She developed cholangiocarcinoma with bone and lung metastases after 9 months of starting treatment and she was deceased. The authors of this study concluded that patients who received etanercept in combination with cyclophosphamide developed more solid neoplasms than those who received placebo [5].

In the literature, the increased risk of malignancy in patients with ANCA vasculitis has been primarily attributed to the carcinogenic effects of cyclophosphamide [6]. The risk is dose dependent. In fact, in a cohort that included 293 patients with GPA, Faurschou et al. showed that a cumulative dose of cyclophosphamide greater than 36 g was associated with a significant increase in the incidence of neoplastic disease [7]. Currently, rituximab represents an effective and less cytotoxic alternative to cyclophosphamide in the treatment of vasculitis. In a recent study that included 323 cases of ANCA vasculitis, Daalen et al. found that after a mean follow-up of 5.6 years, patients treated with cyclophosphamide had a 5-fold greater risk of developing neoplasias compared to those treated with rituximab [8]. However, further large-scale studies are needed to validate these results.

In addition to the cytotoxic effect of immunosuppressive drugs, other theories have been put forward to explain the increased risk of malignancy in patients with ANCA vasculitis. Some authors suggest the presence of underlying immune dysfunction in these patients which may itself be responsible for the increased incidence of neoplasias in this population. Especially since in some studies the diagnosis of the tumor preceded that of vasculitis, which rules out the harmful role of cyclophosphamide [9]. In other circumstances, vasculitis may be indicative of underlying neoplasms. Although the paraneoplastic nature of these vasculitis cannot always be asserted, the parallel evolution of the two pathologies suggests the existence of a causal link. The onset of vasculitis can sometimes precede the discovery of cancer by several months. In this case, the course is generally marked by corticosensitivity with remission of the vasculitis after curative treatment of the underlying tumor. The mechanism of this involvement remains unknown [10].

Conclusion

Vasculitis associated with ANCAs remains severe autoimmune pathologies. Their prognosis has been significantly improved by the introduction of immunosuppressive treatments. However, this has been associated with an increased incidence of neoplastic disease in this population. Biliary tumors are uncommon compared to other types of cancer such as bladder tumors and blood diseases. The peculiarity of this observation was the long latency period

between the diagnosis of vasculitis and that of the bile duct tumor.

References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, et al. (2013) 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 65: 1-11.
2. Sriskandarajah S, Bostad L, Myklebust TÅ, Møller B, Skrede S, et al. (2017) Cancer in ANCA-Associated Glomerulonephritis: A Registry-Based Cohort Study. Int J Nephrol 2017: 6013038.
3. Rahmattulla C, Berden AE, Wakker S-C, Reinders MEJ, Hagen EC, et al. (2015) Incidence of Malignancies in Patients With Antineutrophil Cytoplasmic Antibody-Associated Vasculitis Diagnosed Between 1991 and 2013. Arthritis Rheumatol 67: 3270-3278.
4. Shang W, Ning Y, Xu X, Li M, Guo S, et al. (2015) Incidence of Cancer in ANCA-Associated Vasculitis: A Meta-Analysis of Observational Studies. PloS One 10: e0126016.
5. Stone JH, Holbrook JT, Marriott MA, Tibbs AK, Sejismundo LP, et al. (2006) Solid malignancies among patients in the Wegener's GranulomatosisEtanercept Trial. Arthritis Rheum 54: 1608-1618.
6. Bernatsky S, Ramsey-Goldman R, Clarke AE (2008) Malignancies and cyclophosphamide exposure in Wegener's granulomatosis.J Rheumatol 35: 11-13.
7. Faurschou M, Sorensen IJ, Mellemkjaer L, Loft AGR, Thomsen BS, et al. (2008) Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. J Rheumatol 35: 100-105.
8. van Daalen EE, Rizzo R, Kronbichler A, Wolterbeek R, Bruijn JA, et al. (2017) Effect of rituximab on malignancy risk in patients with ANCA-associated vasculitis. Ann Rheum Dis. 76: 1064-1069.
9. Wester Trejo MAC, Bajema IM, van Daalen EE (2018) Antineutrophil cytoplasmic antibody-associated vasculitis and malignancy.CurrOpinRheumatol 30: 44-49.
10. Hommel C, Rihova Z, Mokaddem F, Libotte B (2014) pANCA-vasculitis associated with rectal adenocarcinoma. Acta Clin Belg 69: 463-466.