Stauffer syndrome : a rare paraneoplastic complication of renal cell carcinoma to be kept in mind. Case report and literature survey

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Abstract

The authors report the case of a 74-years-old woman treated by immunotherapy for a metastatic renal cell carcinoma and having developed an important cholestasis with thrombocytosis, increased CRP, leucocytosis and hypoalbuminemia. Liver remained free of metastases at medical imaging. The diagnosis of a Stauffer syndrome was confirmed by the hepatic biopsy. A complete response of liver disorders was obtained after nephrectomy. From literature survey, Stauffer syndrome should be kept in mind in cancer patients, especially those suffering from a renal cell carcinoma, presenting with cholestasis with no underlying cause. (Acta gastroenterol. belg., **2024,** 87, **40-43**).

Keywords : Stauffer syndrome, renal cell carcinoma.

Introduction

Stauffer's syndrome was initially described in 1961 (1). It is a paraneoplastic syndrome essentially associated to renal cell carcinoma (RCC) and characterized by the occurrence of a hepatic cholestasis in absence of metastases or of obstacles on the bile ducts (2-5). This hepatic injury is reversible after resection of primitive tumour (2-5).

We present the rare case of a 74 years old woman presenting a RCC who developed major cholestasis with jaundice while treated with immunotherapy.

Case Report

A 74-years-old woman consulted in Oncology Unit from 2019, May 26th for a renal tumour complicated by a sella turcica mass (figure 1). The metastatic nature from a clear cell renal cell carcinoma of the parasellar lesion was confirmed by a neurosurgical biopsy on June 6th.

Induction therapy with pazopanib, a multikinase angiogenesis inhibitor, had to be prematurely stopped due to major intolerance with nausea, dysgueusia, complete anorexia, vertigos, increase of blood pressure, major fatigue and asthenia, headaches… After stereotactic radiotherapy on sella turcica metastase, nivolumab immunotherapy was initiated. Nivolumab is a programmed Death-1 (PD-1) inhibitor for targeted

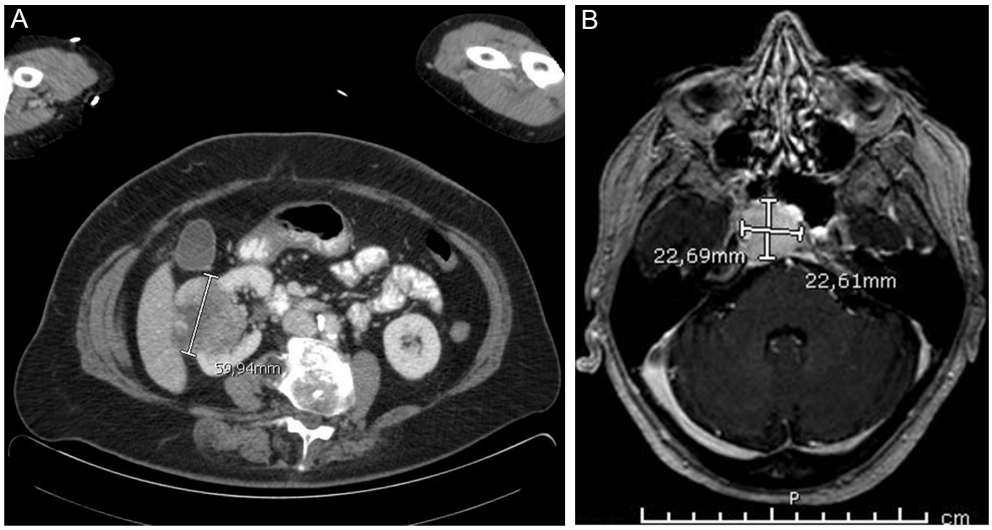

Figure 1. — Imaging at diagnosis. A, Computed tomography of kidney cancer; B, magnetic resonance imaging of sellar metastase.

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immunotherapy in tumor. It binds with high affinity PD1 and blocks its interactions with both PD-L1 and PDL2 and stimulates memory response to antigen-specific T cell proliferation.

After course 2, the patient complained of jaundice, dark yellow urine, decolored stools and pruritis. A mixed alteration of hepatic enzymology with predominant cholestasis (bilirubin, GGT and alkaline phosphatases respectively up to at 4, 13 and 8 times over normal values (Table 1) was recorded. Also was noticed a thrombocytosis at $450.10^3/mm^3$, a hypoalbuminemia (31 g/dl), an increased CRP (38.1 mg/l) and hyperleucocytosis. Etiological searches towards viral or auto-immune syndromes remained negative (ie serology for cytomegalovirus, Epstein Barr virus and hepatitis A,B,C,E, anti-mitochondria, smooth muscles, KLM, SLA/LP, cytosil-1). Anti-DNA antibodies DFS70 were titrated at a 1/160 level rarely associated to an auto-immune disease.

Abdominal echography and CT-scan allowed to exclude metastases or biliary ducts dilation. The hypothesis of a toxic hepatitis due to immunotherapy was retained and corticotherapy at high dosage (1 mg/Kg) was launched on 2019, September 11th. However, after one week, cholestasis continued to worsen.

Thus a hepatic biopsy was performed on 2019, September 18th and revealed a histological aspect of intrahepatic cholestasis with yellowish intrahepatocyte pigmentation and intracanalicular bile thrombi predominant in centrolobular areas (figure 2). No sign of hepatitis but scarce lymphocytes infiltration of main biliary ducts with discrete vacuolisation of their epithelium were also observed (figure 2). These images could have pleaded for a DILI (drug induced liver injury) but their strict limited character excluding portal triad interpellated… Also absence of ductilitis manifestation excluded an auto-immune reaction.

Thus, the aspect was compatible with a possible drug hepatic toxicity or a Stauffer's syndrome.

Diagnosis of Stauffer's syndrome was taken based on clinic consideration, as the corticotherapy had no effect on the hepatic toxicity.

In absence of corticotherapy response, and despite metastatic spread, a nephrectomy was performed on 2019, September 26th. Histology confirmed a clear cell renal carcinoma, Fuhrman grade 3 and pT1bNo stage.

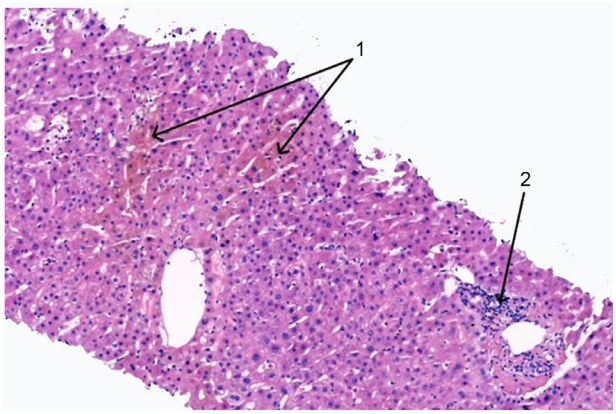

Figure 2. — Histology of hepatic biopsy (hematoxylin eosine). 1, Yellowish intrahepatocytic pigmentation with intracanalicular bile thrombi predominant in centrolobular areas. 2, Visualization of portal triad; some biliary principal conducts surrounded by lymphocytes present a vacuolization of their cytoplasm; no sign of cholangitis; thickness of some portal arteries but veins seem respected.

After surgery a rapid regression with normalization of hepatic biology was appreciated within 8 days (Table 1).

During 5 months, the patient remained in remission. Afterwards despite the reintroduction of pembrolizumab immunotherapy, progression of sellar lesion and appearance of bone metastases will lead to the death in September 2020.

Discussion

Paraneoplastic Stauffer's syndrome, first described in 1961 (1), is principally related to renal carcinomas (of any histological type) with an incidence difficult to evaluate (3-15% according to some estimations?) (2,3). About a hundred cases have been reported (2,3). In rare occurrences, other malignant diseases, such as prostate or bladder cancers, carcinoid tumors, lymphoproliferative disorders, leiomyosarcoma… may engender this syndrome (2,3,6).

Man and woman are equally touched. Typical form behave an anicteric cholestasis with majoration of alkaline phosphatases and GGT and absence of metastases. Frequently, albumine level is lowered, while prothrombine time, sedimentation rate, CRP and platelets counts are increased.

Table 1. — **Evolution of hepatic enzymology**

	AUG, 20th	SEPT, 11th	SEPT, 23th	OCT, 3th	FEB, 19th
AST (U/L)	22	171	528	62	24
ALT (U/L)	22	220	1113	111	24
GGT (U/L)	91	447	1215	386	372
Alk Phosph (U/L)	140	811	1857	586	511
Total Bilirubin (mg/dl)	0.26	4.49	31.27	6.13	0.63
AST, Aspartate transaminase; ALT, Alanine transaminase; GGT, Gamma-glutamyl transferase, Alk Phosph, Alkaline phosphatase.					

More recently a variant form occurring in 15% cases with hyperbilirubinemia, icteris, pruritis, dark urine and acholic stools has been described (2,3,6). Our case presented these last characteristics associated with the majoration of hepatic enzymes and also an increased CRP.

Moreover, a hepato-splenomegaly may also be observed in some cases (1-4).

Not all criteria are present in every patient but some are fundamental to establish the diagnosis. A cholestatic hepatic dysfunction must be assessed in absence of liver metastases or other causes of hepatic alterations (obstacle on biliary routes, drug toxicity, viral damage...). Of interest, only a few subjects have benefited from a hepatic histology. As in our subject, no specific feature of the Stauffer syndrome was reported. Isolated cholestasis with its more or less important repercussions on liver parenchyma remains the prominent observation (1-4,6).

Perturbation of hepatic tests will be reversible after primary tumor resection especially among non-metastatic subjects (2,3). Our patient, though metastatic, benefited from nephrectomy which has brought to normalization of hepatic function; this allowed us to conclude to a true Stauffer syndrome.

Physiopathology of this syndrome is not yet fully understood. The actual main hypothesis is based on interleukine 6 (IL6) release from renal tumor (7,8). This will induce an increase of protein C reactive (CRP) and haptoglobin leading to an inhibition of expression of bilirubin-carrying genes inducing cholestasis (7,8). IL-6 is a multifunctional cytokine implicated in immune response and hematopoiesis (7). It is involved in pathogenesis of cancers (renal one among others) contributing to tumoral progression (8). This impact is mediated through link of IL6 to its receptor composed of a sub-unit fixation to ligand called gp80 and another subunit transducing gp130 signaling (7).

Soluble form of ligand (sIL-6R) leads to activation of Janus kinases (JAK) and gp130, thanks to their phosphorylation inducing further signal pathways, principally the STAT route (signal transducers and activators transcription) regulating cell survival and proliferation (7).

Significant differences in overall survival after surgery have been shown according to tumor burden (≥8 cms), presence of synchronous metastases, high nuclear grade, proliferation index KI67 (≥4%), IL6 in situ and seric concentrations of IL6, SIL-6R and CRP (2,3,8). Seric titration in IL6 was correlated to size and stage of primary tumor (8). Unfortunately, titration of IL6 in serum or its determination on hepatic sample or kidney tumour was not possible in our routine practice.

Treatment of Stauffer's syndrome is based on the primary disease control. In localized forms of RCC, nephrectomy is the first issue (2-5). In metastatic forms, by now, with development of effective systemic therapies, surgery has not remained systematically standard treatment (2,3).

However tyrosine kinase inhibitors (TKIs) generally proposed in first line treatment of metastatic or advanced RCC (10) are contraindicated in presence of an hepatic dysfunction (ie hyperbiluruninemia), thus in case of confirmed Stauffer syndrome (2,3). Immunotherapy is a new therapeutic option but its efficacy and safety in Stauffer's syndrome is not well documented. In the literature, only one case of RCC complicated of a Stauffer syndrome treated temporally with immune treatment (nivolumab and ipilimumab) is recorded (10). A local regression of primary tumour was observed but without any effect on cholestatis. A further surgical resection permitted normalization of hepatic parameters (10). Of interest, in 2003, Karakolios et al. have observed improvement of a Stauffer's syndrome after medical treatment for an advanced prostate cancer (11). Gougelet et al. also proposed IL6 targeted therapies in those tumoural situations (12).

Normalization of hepatic alterations after anti-IL6 has occasionally been reported (12).

As observed in the majority of cases in the literature, nephrectomy allowed normalization of hepatic enzymes in our patient.

Immunotherapy with anti-PD1 and anti-PDL1 agents can promote the appearance of various paraneoplastic syndromes or worsen pre-existing ones within a median of 1.4 months after initiation (13). Described cases are essentially paraneoplastic neurological syndromes; no Stauffer syndrome was observed (13).

Thus, our knowledge on immunotherapy and paraneoplastic complications are limited. According to our clinical case and in correlation with the previously described one, immunotherapy seems to be unable to prevent Stauffer's syndrome. However, the data are too scarce to allow definitive conclusion.

Conclusion

Stauffer's syndrome must be evoked in face of an unexplained cholestasis in peculiar among those patients suffering from a RCC. Physiopathology of this paraneoplastic event remained in part unexplained. The first treatment to be considered is resection of primary tumour especially in non-disseminated presentations. Immunotherapy impact on Stauffer syndrome is not yet known but our experience led us to estimate that it will not prevent its development.

Conflict of interest

The authors declare no conflict of interest.

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