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REVIEW

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Stauffer syndrome: a comprehensive review of the disease and diagnostic plan proposal

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Abstract

Stauffer syndrome, first described by Herbert Stauffer in 1961, is a hepatic paraneoplastic syndrome characterized by multiple extrahepatic malignancies, most commonly renal cell carcinoma. The syndrome manifests a wide range of symptoms caused by various pathophysiological mechanisms and presents with abnormalities in liver function tests in either cholestatic or non-cholestatic patterns.

Stauffer's syndrome is classified into two types: classical and jaundice variants. Some crossovers continue to occur, complicating the diagnosis of such a rare and frequently missed syndrome, which can be the only diagnostic clue for the retrograde detection of a hidden malignancy.

To bridge the gap regarding such an important, but still unrecognized, syndrome, not only did we thoroughly cover what had previously been proposed in the literature, but we also proposed a diagnostic protocol based on multicenter experience with such a rare disease.

Keywords: Stauffer syndrome, Paraneoplastic, Hepatic dysfunction, Cholestasis, Jaundice, Tyrosine kinase, IL-6

Introduction

Stauffer syndrome is a rare paraneoplastic disorder that affects the liver and is associated with RCC. It is far less common in other malignant neoplasms such as leiomyosarcoma, angiosarcoma, malignant histiocytoma, prostate carcinoma, and bronchial adenocarcinoma [1–4]. Stauffer syndrome is a cholestatic pattern of hepatic dysfunction signs and symptoms with associated abnormalities in liver function tests. This dysfunction is not caused by tumor infiltration of the liver or intrinsic liver disease, but rather by the presence of a paraneoplastic syndrome that causes abnormal bile flow and biliary tract affection through a variety of proposed mechanisms [5]. In cases of idiopathic cholestatic or atypical liver disease, the diagnosis of Stauffer's syndrome should be considered.

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Discussion

Stauffer syndrome is a rare paraneoplastic disorder characterized by hepatic biliary involvement in the presence of visceral malignancy, most commonly renal cell carcinoma. Multiple abnormalities, including hypoalbuminemia, hypergammaglobulinemia, high alkaline phosphatase (ALP), prolonged prothrombin time (PT) without a history of intrinsic liver disease or Hepatic metastasis, and the presence of a concomitant renal cell carcinoma, were observed in the first five initially reported cases. Both liver function tests (LFTs) and clinical signs and symptoms returned to normal following tumor resection [5, 6].

The incidence of the syndrome in patients with RCC varies between 3% and 6%. Although the hepatic dysfunction resolves after primary tumor resection. However, the development of SS in an RCC patient has been associated with a poor prognosis due to deterioration of hepatic functions or due to the advanced stage of the primary tumor when the diagnosis is concealed until the time of diagnosis of that associated paraneoplastic syndrome [7–10].

Pathophysiology

The underlying pathophysiology of this paraneoplastic manifestation has yet to be determined, but three mechanisms have been proposed. The most widely accepted hypothesis proposes a link and a possible role for primary tumor interleukin-6 overexpression [11–13]. Cholestasis and hepatic dysfunction are believed to be secondary to IL-6's pro-inflammatory activity in Stauffer syndrome. IL-6 increases C-reactive protein and haptoglobin levels and has been shown to inhibit hepatobiliary transporter gene expression. All these factors contribute to biliary outflow impairment [11].

A study found that patients with Stauffer's syndrome had their biochemical abnormalities reversed after receiving anti-IL-6 monoclonal antibodies. However, such findings did not provide a definitive definition, but a speculative one. Other humoral mediators have been implicated; this was due to the emergence of increased activity of these mediators when the tested rational association between them was made, resulting in hepatic and hematopoietic compromise [11].

The colony-stimulating factor is another proposed mechanism (CSF). Athymic mice were given renal cancer cells extracted from an SS patient. This resulted in hepatic affection and splenomegaly. Furthermore, polysulphones naphthyl urea suramin, a known CSF inhibitor, improved experimental mice [14]. The third and least supported hypothesis proposed an underlying autoimmune etiology in these patients [15].

Clinical features

The classical variant presents with flank mass, loin pain, and hematuria, with an associated cholestatic abnormality in liver function tests such as elevated alkaline phosphatase, erythrocyte sedimentation rate, α-2-globulin, and γ-glutamyl transferase, hypoalbuminemia, thrombocytosis, prolongation of prothrombin time [16–25]. An extremely rare and uncommon jaundice variant with hyperbilirubinemia, hepatosplenomegaly, abnormal coagulation profile, jaundice, choluria, and pruritus has also been reported. Crossovers in patients' presentations, on the other hand, have been reported.

This crossover is distinguished by mild epigastric and left upper quadrant tenderness, as well as mildly elevated liver function tests (LFT), erythrocyte sedimentation rate (ESR), and C-reactive protein. On abdominal CT, there was a renal mass with normal liver size and no metastasis. Mild pruritus, dark urine, and stool discoloration are also reported by all patients.

The table below summarizes the laboratory findings of most reported cases to highlight the differences between the two variants [25] (Fig. 1).

Diagnosis

Stauffer's syndrome currently lacks diagnostic criteria but remains a viable diagnosis when underlying renal malignancy is present in the context of cholestatic liver damage.

The first step toward diagnosis should be a baseline liver function test, with particular attention paid to bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase levels (GGT). A cholestatic elevation of LFTs indicates a defective flow of bile from the liver into the duodenum via the bile ducts and the ampulla of Vater. ALT can be elevated in the later stages of severe cholestasis, but the rise in ALP and/or GGT will exceed any rise in ALT [6–8].

The synthetic function of the liver should be assessed using both prothrombin time (PT) and international normalized ratio (INR). Both can be elevated since decreased bile flow reduces fat-soluble vitamin absorption and impairs the liver's subsequent clotting factor synthesis, raising the PT.

Clinical/analytical parameters	Stauffer's syndrome classic description	Stauffer's syndrome (jaundice) variant description
Alkaline phosphatase	High	High
γ-Glutamyl transferase	High	High
Albumin	Low	Low
Erythrocyte sedimentation rate	High	High
α-2-globulin	High	High
Platelets	High	High; thrombocytopenia described in one case
Prolongation of prothrombin time	Present	Present
Hepatosplenomegaly	Present	Absent/present
Hyperbilirrubin	Absent	Present
Jaundice	Absent	Absent/present
Urinary hyperpigmentation	Absent	Present
Pruritus	Absent	Present
Resolution after ressection of primary tumor	Yes	Yes

Fig. 1 Clinical/analytical parameters for Stauffer's syndrome variants

A complete liver function panel should be performed to rule out any other underlying abnormality causing acute liver damage, and consultation with the gastroenterology team is recommended. Imaging should be used to confirm hepatosplenomegaly and rule out other causes, such as metastatic disease [7, 23].

An initial ultrasound of the biliary tree and liver should reveal no signs of malignancy, common bile duct (CBD), or hepatic duct dilatation.

Magnetic resonance cholangiopancreatography (MRCP) can aid in the detection of underlying CBD stones or other causes of CBD obstruction. which would be useful If a prior cholecystectomy or ultrasound confirmed CBD dilatation/cholelithiasis.

The renal mass is delineated by a contrast CT scan of the abdomen and pelvis and any underlying hepatic, pancreatic or metastatic malignancy will be further evaluated. CT imaging alone is sufficient to rule out other causes of liver derangement. As with any malignancy, complete staging scans are discussed at the multidisciplinary team (MDT) meeting to decide on further management and whether we should be driven by distinctive clinical presentation intensity and or major lab elevations in consideration of one management approach over the other or even palliative versus more invasive intervention [24, 25].

There should be a high clinical suspicion and understanding of the disorder; however, troubling clinical signs and symptoms that may guide the diagnosis of Stauffer syndrome or other distinct diagnoses are suggested in our literature review. We propose a preliminary diagnosis guideline protocol to be validated further by additional trials (Fig. 2). The only major drawback is the unusual nature of the condition and the scarcity of cases documented.

Further clinical studies are encouraged to cover the whole side of such a rare and overlooked syndrome to ensure proper diagnosis and management avoiding its fatal consequences. Renal cell carcinoma in the presence of elevated liver enzymes presenting in either cholestatic or non-cholestatic patterns should prompt the physician to proceed to the next step, which is a more detailed search of the patient's medical history for an underlying cause. If no underlying cause is discovered after ruling out NASH, alcoholism, and metabolic syndrome. A negative ultrasound, CT, or MRCP can increase the likelihood of Stauffer syndrome.

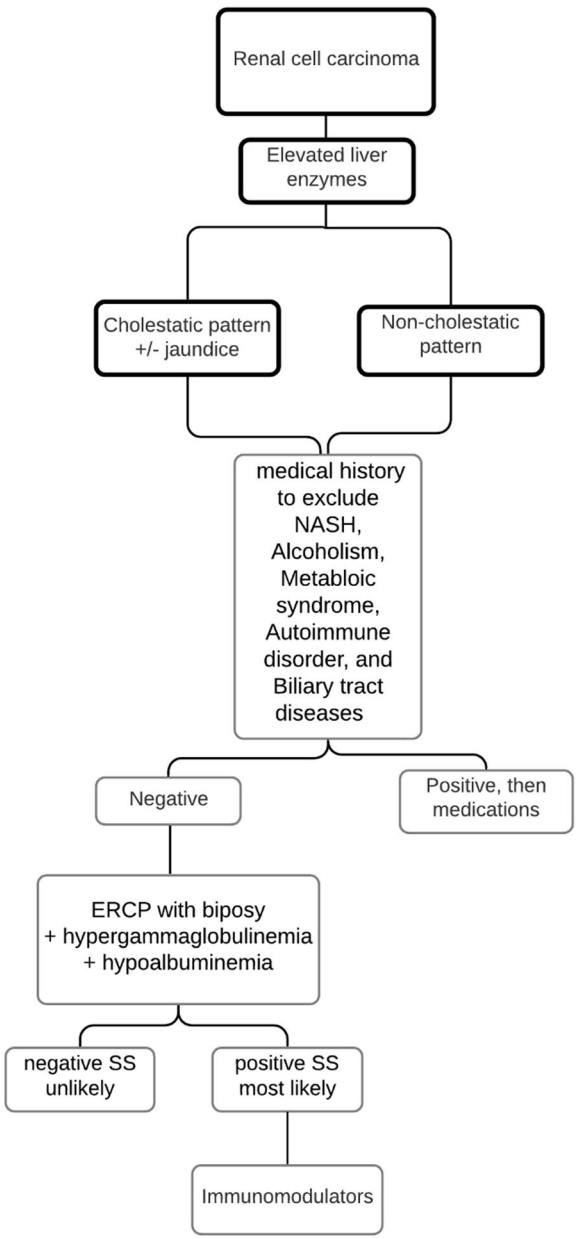

Fig. 2 Stauffer syndrome diagnostic plan proposal. NASH, non-alcoholic steatohepatitis; ERCP, endoscopic retrograde cholangiopancreatography; SS, Stauffer's syndrome

Management

Disease management remains an MDT decision, but it primarily consists of resection of the occult renal tumor, which is the source of the paraneoplastic syndrome, via nephrectomy after preoperative symptomatic care, such as ursodeoxycholic acid, cholestyramine, and avoidance of hepatotoxic medications.

In recent years, there has been a significant shift in the treatment of metastatic RCC associated with Stauffer syndrome. Whereas neoadjuvant cytoreductive nephrectomy has been the standard of care in RCC, recent evidence from the CARMENA and SURTIME trials suggests that upfront nephrectomy may harm some intermediate- and poor-risk metastatic RCC patients [26].

Treatment guidelines recommend starting with a systemic therapy litmus test. For patients with Stauffer's syndrome, the treatment paradigm becomes more complex. Multiple systemic therapies are approved for first-line treatment of RCC, however, all the regimens target angiogenesis via TKIs. TKIs harbor their own risk of hepatotoxicity, and their use is contraindicated in the setting of hyperbilirubinemia. Immune checkpoint blockade (ICB) represents a novel and feasible treatment option available in the current treatment landscape of metastatic RCC [27–30].

Conclusion

Stauffer syndrome is a reversible paraneoplastic hepatic dysfunction that can occur in conjunction with a variety of tumors but is most associated with RCC. In cases of idiopathic cholestatic or otherwise atypical liver disease, the diagnosis of Stauffer's syndrome, as well as the possibility of an underlying occult malignant tumor, should always be considered. Because the disease can be used to diagnose an occult malignancy, a high level of clinical suspicion is required.

Abbreviations

LFT: Liver function test; RCC: Renal cell carcinoma; IL-6: Interleukin-6; CSF: Colony-stimulating factor; INR: International normalized ratio; PT: Prothrombin time; TKI: Tyrosine kinase inhibitors; CBD: Common Bile duct; NASH: Nonalcoholic steatohepatitis; CT: Computerized tomography; MDT: Multidisciplinary team; ERCP: Endoscopic retrograde cholangiopancreatography; MRCP: Magnetic retrograde cholangiopancreatography.

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Authors' contributions

All the authors have shared work in collecting, analyzing, and writing the research paper. AA and SE were major contributors in writing the manuscript, while D.M. and M.E. were major contributors in collecting needed information from different centers. The manuscript did under the supervision of AI. The authors read and approved the final manuscript.

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Declarations

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Competing interests

The authors declare that they have no competing interests.

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