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Case report

Surgical management of portal hypertension in Felty's syndrome: A case report and literature review☆

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***Background/Aims*: Bleeding esophageal varices are a common complication of portal hypertension in patients with underlying liver disease. Often patients with hepatic cirrhosis have hypersplenism with thrombocytopenia and leukopenia. Felty's syndrome is a disorder where patients with rheumatoid arthritis develop splenomegaly, neutropenia, and on rare occasions, portal hypertension without underlying cirrhosis.**

***Methods*: We present a case of a patient with portal hypertension secondary to Felty's syndrome and discuss the importance of recognizing this condition since the treatment of choice is surgical management with splenectomy. A review of the literature and underlying liver histologic features are discussed.**

***Results*: Medical and surgical management of patients with Felty's syndrome is different from those with portal hypertension due to cirrhosis.**

***Conclusion*: Splenectomy is the treatment of choice for complications of portal hypertension in patients with Felty's Syndrome.**

***Keywords*: Varices; Portal hypertension; Splenectomy**

1. Case report

A 53-year-old Caucasian male presented to the emergency department with hematemeis. His medical history was significant for rheumatoid arthritis, benign prostatic hypertrophy, GERD, hyperlipidemia and COPD. His medications included etodolac, fenofibrate, rabeprazole, tiotropium, hydroxychloroquine and occasional over the counter NSAIDs. He denied drug or alcohol abuse and had no prior episodes of gastrointestinal bleeding. Family history was pertinent for his father having died with idiopathic cirrhosis. The physical examination revealed resting tachycardia, lower extremity petechiae, epigastric tenderness, splenomegaly, and hemoccult positive stool. Abnormal laboratory tests showed a hemoglobin of 11.1 g/dl and platelet count of 73,000/μl. Liver profile and coagulation times were normal.

An upper endoscopy was performed revealing grade 3 esophageal varices (Fig. 1A) extending from the gastroesophageal junction (40 cm) to 28 cm with stigma of recent bleeding and a mosaic appearance was seen in the gastric mucosa consistent with portal gastropathy (Fig. 1B). Variceal ligation was performed with a

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Abbreviations: GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; NSAID, nonsteroidal antiinflammatory drugs; RA, Rheumatoid arthritis; NRH, nodular regenerative hyperplasia; IPH, idiopathic portal hypertension; H&E, hematoxylin and eosin.

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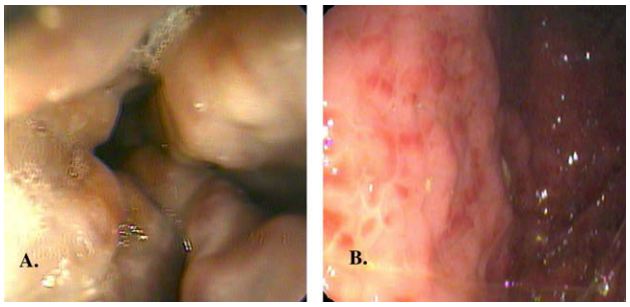

Fig. 1. Photographs taken during initial upper endoscopy revealed (A) grade 3 esophageal varices with stigmata of recent bleeding and (B) congestive portal gastropathy.

banding device. Abdominal venous ultrasound revealed patent portal and superior mesenteric veins and normal hepatic. Liver biopsy was performed and revealed macrosteatosis, mild portal inflammation, focal mild fibrous expansion, normal sinusoids, and no evidence of cirrhosis (Fig. 2). Transhepatic wedge pressures were performed and were consistent with significant portal hypertension (the sinusoidal pressure, i.e., difference between the mean right hepatic wedge pressure and the mean right atrial pressure was 11 mm Hg; the mean wedge pressure was 18 mm Hg). The patient was referred to surgery for splenectomy. Splenic artery

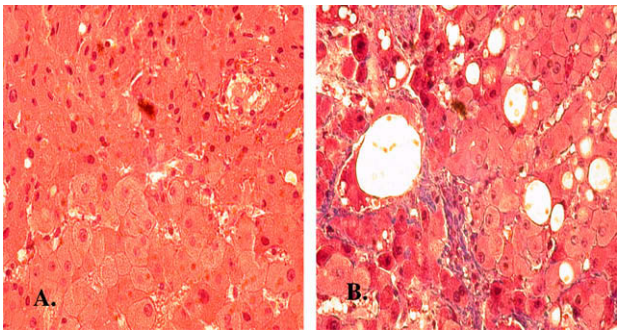

Fig. 2. Histology sections of the liver revealed macrosteatosis, mild portal inflammation, and normal sinusoids on the hematoxylin and eosin stain (A) and focal mild fibrous expansion without evidence of cirrhosis on the trichrome stain (B).

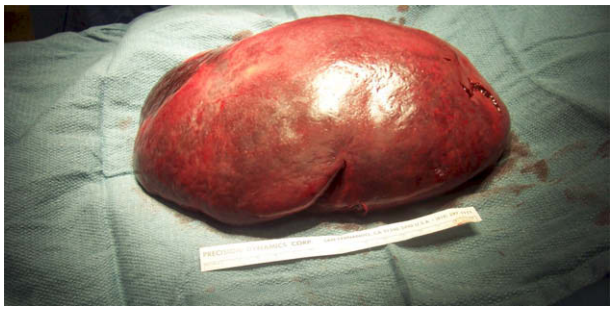

Fig. 3. A massively enlarged spleen was removed at surgery weighing 1875 g and measuring 12.2 × 1.8 × 2.5 cm.

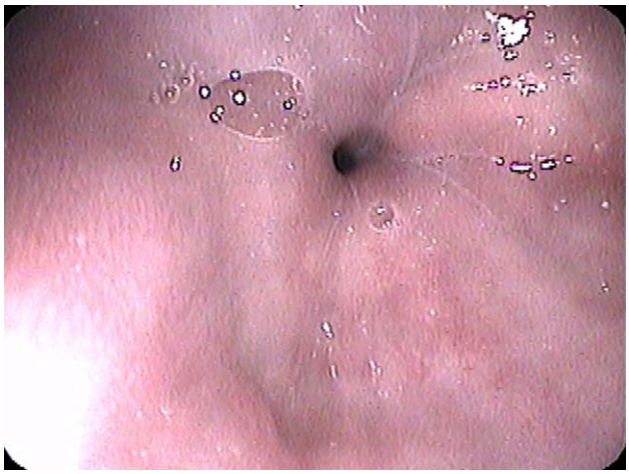

Fig. 4. Six months post-splenectomy repeat upper endoscopy showed a normal distal esophagus with complete resolution of esophageal varices.

embolization was performed preoperatively. At surgery the liver appeared normal and a 1875 g (12.2 × 1.8 × 2.5 cm) spleen was removed (Fig. 3). Follow-up endoscopy post-operatively revealed no evidence of esophageal varices or portal gastropathy (Fig. 4).

2. Literature review

2.1. Felty's syndrome overview

Felty's syndrome, a well-described triad of neutropenia, splenomegaly, and rheumatoid arthritis (RA), has made multiple appearances in the literature since it was described in 1924 [1]. Less than 1% of patients with rheumatoid arthritis (RA) have Felty's syndrome, and these patients frequently have severe joint destruction, a higher occurrence of rheumatoid nodules, lymphadenopathy, hepatic pathology, vasculopathy, leg ulcers and other recurrent infections. A high percentage of those with Felty's syndrome (78–90%) have the HLA-DR4 antigen (compared to 70% of typical RA patients and 30% of controls), suggesting a genetic component to this syndrome [2–4].

2.2. Liver histology in Felty's syndrome

Several authors have reported varices in association with Felty's syndrome, with varying underlying liver pathology, most frequently nodular regenerative hyperplasia (NRH) [5–12]. Other liver abnormalities found on biopsy include: diffuse lymphocytic infiltration in the sinusoids and Kupffer cell prominence, periportal fibrosis, macronodular cirrhosis, and "nodules" without fibrosis or lobular disruption [5]. No correlation between transaminase abnormalities and histology could be made [5]. In 1974, Blendis et al. found what seemed to be a pattern in Felty's associated liver pathology: they reported 5 patients with Felty's syndrome who had hepatic nodular

regenerative hyperplasia (NRH) [6]. Sweeney described a case with Felty's syndrome showing hyperplastic liver cells with atrophic double liver cell plates surrounding the nodular zones of the NRH [11]. Sweeney claimed the "double cell plates suggested that the liver underwent generalized hyperplasia before nodule formation occurred," and that drugs used in treatment of RA could have spurred hepatocyte growth. Furthermore, he suggested that NRH could compress intrahepatic venous radicals and sinusoids, leading to portal hypertension[11]. Some have offered possible explanations for the development of NRH, including compression of intrahepatic vessels by regenerating nodules, obliterative portal venopathy caused by diffuse intrahepatic microthrombi from platelet activation [13,14], or similar changes in blood flow secondary to deposition of immune complexes leading to regenerative nodules [14]. Several suggested that vasculitis may play a role in the development of NRH [15,16]. Rau suggests that abnormal hepatic histology, enlarged lymph nodes, and splenomegaly should be "considered as organic manifestations of rheumatoid arthritis" noting that "a reaction of the reticuloendothelial system with its organs (lymph nodes, spleen, bone marrow and Kupffer cells) is not uncommon in rheumatoid arthritis [9]."

In addition to Felty's syndrome the histologic abnormality of NRH has also been reported in CREST syndrome, polycythemia vera, collagen vascular disorders, lymphoproliferative disorders and malignant neoplasms and possibly long term use of corticosteroids, oral contraceptive pills, and antineoplastic/immunosuppressive drugs [17–19]. The finding of cirrhosis in a patient with Felty's syndrome is rare [20].

2.3. Increased splenic blood flow and portal hypertension

Splenomegaly from various causes may result in elevated portal vein pressures by increased total blood flow through the splenic artery. Klofkorn reported marked decline in portal pressures in patients with esophageal varices and Felty's syndrome treated with splenectomy [8]. This surgical approach prevented future episodes of gastrointestinal bleeding in their patients. In similar cases, Reisman and colleagues suggested that the portal hypertension was a direct result of increased splenic blood flow [21]. Some argue that the portal hypertension in Felty's syndrome results from a combination of increased splenic blood flow and postsinusoidal resistance from microthrombosis [14,22]. These observations beg the question of whether NRH is one end of a continuum of hepatic changes related to the splenomegaly seen in Felty's syndrome and if these changes can constitute a separate contributing factor to portal hypertension, in addition to increased splenic blood flow alone. The question remains of whether increased splenic blood flow alone could induce histologic hepatocellular changes that in turn lead to portal hypertension or whether hepatic pathology (created by another stimulus in patients with RA with or without Felty's) could, in conjunction with increased blood flow from splenomegaly, lead to portal hypertension in these patients. Although splenectomy with or without splenorenal shunt [13] may prevent further bleeding from esophageal varices, some advocate conservative medical management [23] especially in elderly patients.

2.4. Cirrhosis-induced portal hypertension versus Felty's Syndrome portal hypertension:

In contrast to cirrhosis patients, those with bleeding from esophageal varices secondary to Felty's syndrome do not develop encephalopathy. Also unlike subjects with cirrhosis, splenectomy decreases the portal hypertension and results in decompression of esophageal varices in patients with Felty's Syndrome. Thorne and colleagues reported "the association of abnormal liver test results with abnormal serologic variables may indicate those patients likely to have abnormal liver histologic features." However, transaminase abnormalities are not a reliable indication of abnormal liver histology and our patient did not have any transaminase abnormalities. Therefore, the liver abnormalities may be detectable only by liver biopsy [12]. Most patients with cirrhosis as the etiology of portal hypertension often also have evidence of synthetic hepatic dysfunction, such as hypoalbuminemia or prolonged coagulation time. A clue that our patient did not have cirrhosis was the lack of abnormal hepatic blood tests.

Nakanuma et al. suggest that "unusual histologic lesions in the livers of idiopathic portal hypertension (IPH) patients with autoimmune disease may represent an accentuated immunologic reaction inherent in IPH, or that such cases may be an abortive or incomplete form of primary biliary cirrhosis or nodular regenerative hyperplasia of the liver [24]." Gento Peña et al. [25] reported a case in addition to Harris's where the patient had RA only with NRH and marked portal hypertension and elevated transaminases [25]. Gortisas et al. add another report of NRH in a patient with RA without Felty's [26]. Taken together, these reports do support the idea that it is not splenomegaly alone (which exists in Felty's syndrome) that is causing NRH and/or other hepatic changes that lead to varices. Perhaps another process that exists in both RA and Felty's (and perhaps is accentuated in Felty's) is affecting the liver. Perhaps this process, especially in combination with splenomegaly (but not requiring splenomegaly), leads to portal hypertension and varices in these patients.

More recent discussion regarding splenomegaly raises interesting points and supports the idea that, though splenomegaly may not be solely responsible for the por-

tal hypertension and varices seen in Felty's, its possible role cannot be totally discounted. A report on tropical splenomegaly syndrome [27] (which seems to be related to malaria exposure) noted asymptomatic esophageal varices in 12 of 68 patients, all with Hackett's stage 4 or 5 splenomegaly (8 of 12 were multiparous females). Endoscopy seemed to indicate low bleeding risk. None had collaterals connected to the portal system.

A recent interesting addition to the literature by Sema et al. [28] reports a case of Felty's syndrome with chronic hepatitis and compatible autoimmune hepatitis in which the patient had a contracted liver, ascites, tortuous enlarged splenic vein, and splenomegaly and esophageal varices with subsequent banding [28]. The patient died from hepatic failure with encephalopathy. Needle biopsy of the liver showed chronic hepatitis, normal lobular architecture, fibrosis and piecemeal necrosis, portal inflammation, lymphocytes and plasma cells.

The authors argue that the outcome for this patient was a combination of factors: "Splenomegaly in patients with Felty's syndrome might be due to expansion of the sinusoidal pulp, as indicated by wider separation of the periarterial lymphoid sheaths and hyperplastic germinal center. In the present case, we are convinced that increasing blood flow to the spleen due to splenomegaly caused portal hypertension, congestion of blood within the liver, and chronic hepatitis gradually worsened to liver failure [28]."

Cohen et al. add another interesting report of hepatic pathology in Felty's Syndrome, a 68 year old woman with massive hepatomegaly and biopsy of liver showed preserved hepatic architecture, significant sinusoidal infiltration with mature lymphocytes in centrilobular and periportal zones, minimal portal triad expansion with mature lymphocytes with limiting plate intact, minimal cholestasis present in centrilobular areas, no fibrosis and no nodule formation [29]. There is no mention of portal hypertension in this patient, and the authors cite Blendis' previous report of 5 cases of sinusoidal lymphocytosis of the liver in Felty's Syndrome, noting that one had portal hypertension, but in the presence of portal fibrosis additionally. The authors also comment: "Sinusoidal lymphocytosis of the liver in Felty's syndrome bears a close relationship to the liver histology found in idiopathic tropical splenomegaly syndrome [which] is believed to be the result of a chronic immune response to Plasmodium malaria. It is therefore tempting to speculate that sinusoidal lymphocytosis of the liver in Felty's syndrome might also be related to immunologic factors."

3. Conclusion

Felty's syndrome is a rare complication of rheumatoid arthritis which can rarely lead to portal hypertension and varices. In patients with this complication, nodular regenerative hyperplasia is the most common underlying liver pathology. More rarely, this complication has been reported in patients with much more subtle changes or even normal liver biopsies. Our patient adds another to the small number of such case reports. It has been noted several times in the literature, however, that percutaneous needle biopsy and even wedge biopsy may not always capture the characteristic architectural changes of NRH. One has even suggested that reticulin staining, and not H&E alone may be necessary to visualize these changes. Therefore, the cases of NRH may be underestimated, and there is a small possibility that nodular changes could be present but not proven in our patient.

The possibility remains as well that the subtle changes noted in our patient and in other patients who have had portal hypertension without NRH lie at one end of a continuum of hepatic pathology effected by some process found, or perhaps, accentuated in Felty's syndrome. Of note, more evidence is building for similar liver histologic changes (including NRH) in RA without Felty's and other rheumatologic conditions as well. It would seem that the liver is being affected in these diseases and causing, or contributing to, the development of portal hypertension in the absence of a component of splenomegaly, though some studies suggest that splenomegaly can affect the liver in mechanisms apart from just increasing flow. It is likely that the combination of these hepatic changes with the presence of splenomegaly work together to increase the likelihood of developing portal hypertension and even varices in Felty's syndrome.

However, the seemingly successful treatment of varices with splenectomy in several patients, including ours, would support the idea that increased splenic and thus portal blood flow is a causative factor of portal hypertension. It may be that, in patients with varices and portal hypertension, shunt procedures are advisable as well (especially if another component in addition to increased splenic and portal flow is believed to play a role). One could argue that our patient's esophageal varices resolved because of banding, apart from splenectomy. However, the patients gastric varices underwent no direct intervention and follow-up endoscopy post splenectomy showed improvement in portal gastropathy.

Our case brings an entry to the more narrowly focused dialog on the liver pathology seen in Felty's patients who present with esophageal or gastric varices and the role of splenectomy and shunt as treatment. Our patient's subtle changes on liver biopsy with associated portal hypertension and varices place him in the company of only a few other cases that we found on extensive review of the literature.

In our review of the literature, we did not find any studies evaluating the benefit of screening patients with Felty's syndrome for portal hypertension in an effort to prevent bleeding complications, though the sentiment for possible screening has been occasionally suggested in the literature. Perhaps the measurement of portal pressures, screening liver biopsy, or even endoscopy in some cases could prevent fatal complications in patients with Felty's syndrome. A study examining this question may be beneficial.

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