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IgG4 plasma cell neoplasm in liver transplant biopsy masquerading as rejection

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ABSTRACT

IgG4 plasma cell neoplasm and myeloma are rare disease entities, not associated with systemic fibroinflammatory IgG4 related disease. We herein present a case of IgG4 plasma cell neoplasm in a liver transplant biopsy. A 55 year old female was treated with living donor transplant and had a complicated post-operative course. Three months post-transplant, she presented with small for size syndrome, biliary stricture, and inferior vena cava stenosis. Concomitant liver biopsy revealed mild acute cellular rejection with central perivenulitis pattern, and mild centrilobular fibrosis. She was treated with steroids which resulted in improvement of liver enzymes. Seven months post-transplant, she presented with subtherapeutic prograf levels and cholestatic pattern of elevated liver tests. ERCP revealed a stone which was removed. Hematological evaluation revealed an abnormal serum protein electrophoresis (SPEP). Monoclonal IgG kappa was elevated along with mildly elevated free Kappa/Lambda ratio. She was followed up and readmitted two months later for worsening liver function tests. The liver biopsy showed monotypic Kappa-and IgG4-restricted plasma cell infiltrates in portal, periportal, sinusoidal and centrilobular regions, compatible with plasma cell neoplasm. In the clinical context of positivity for a serum M-spike, the monoclonal hepatic infiltrates were deemed consistent with a Kappa-and IgG4-restricted plasma cell neoplasm. Patient was treated with pulsed steroids, and liver function tests subsequently downtrended. She was followed up by Hemoncology, and the treatment plan included carfilzomib-based induction therapy and dexamethasone to prevent end-organ damage from evolving myeloma. In the meanwhile, she developed acute appendicitis, underwent appendectomy, and passed away in the post-operative period.

1. Introduction

IgG4 plasma cell myeloma is a rare disease entity. The neoplastic plasma cells in myeloma undergo somatic hypermutation and class switch recombination. They secrete antibodies, most frequently IgG isotype, contributing to paraproteinemia in the serum, and a large monoclonal spike on serum protein electrophoresis (SPEP). The few previously reported cases of IgG4 plasma cell myeloma have been diagnosed by bone marrow evaluation. A single case with involvement of thyroid gland has also been reported. IgG4 myeloma is generally not associated with systemic fibroinflammatory IgG4 related disease. To our knowledge, the present case is the first case of IgG4 plasma cell myeloma presenting in a liver transplant biopsy [1–5].

2. Case presentation

A 55 year old female who presented with alcoholic liver cirrhosis, ascites, hepatic hydrothorax, and portosystemic encephalopathy. She was treated with living donor liver transplant from her son. A liver biopsy taken two weeks after transplant surgery revealed mild acute cellular rejection and moderate preservation injury. The post-operative course was subsequently complicated by small for size syndrome, intramuscular hematoma along with VRE bacteremia, biliary stricture, and inferior vena cava stenosis. The biliary stricture and inferior vena cava stenoses were stented three months after transplant. Concomitant liver biopsy revealed late allograft rejection with perivenular plasma cell infiltrates, and mild centrilobular fibrosis. The plasma cells were polyclonal with unremarkable kappa lambda ratio. C4d immunostain was negative. She was diagnosed with late allograft rejection and treated with steroids, which resulted in improvement of liver enzymes.

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Four months later she presented with subtherapeutic prograf levels and cholestatic pattern of elevated liver tests. ERCP revealed intact stent within the stricture, and a stone both of which were removed. However, the liver function tests worsened subsequently, with no detectable abnormality on repeat ERCP, but improvement with antibiotics. Hematological evaluation revealed an abnormal serum protein electrophoresis (SPEP). Monoclonal IgG kappa was elevated along with mildly elevated free Kappa/Lambda ratio. Bone marrow biopsy was deferred due to patient preference. She was readmitted two months later, ie nine months post transplant for worsening liver function tests and another liver biopsy was performed. The biopsy revealed moderate centrilobular, intrasinusoidal and portal/periportal inflammatory infiltrate comprised predominantly of plasma cells. Mild interface activity and lobular unrest along with centrilobular hepatocyte dropout and clusters of ceroid-laden Kupffer cells were present. The portal tracts revealed multifocal bile duct injury. Patchy minimal portal vein endotheliitis was seen (Fig. 1). IgG4 highlighted upto 35 plasma cells per high power field at the hot spots in portal tracts (Figs. 2 and 3). The IgG4/ IgG ratio is approximately 30%. Immunohistochemistry showed atypical kappa predominant plasma cells (Fig. 4). CD3 highlighted a few small T cells. CD20 highlighted rare small B cells. The findings were most compatible with involvement by plasma cell neoplasm. The serum protein electrophoresis (SPEP) evaluation revealed increased IgG and a high kappa lambda ratio. In the above context and presence of a serum M-spike, the hepatic infiltrates were deemed consistent with a Kappa-and IgG4-restricted plasma cell neoplasm. Epstein Barr virus early antigen (EBNA) and in-situ hybridization tests (EBER ISH), Herpes Simplex virus and Cytomegalovirus DNA PCR were negative. Patient was treated with pulsed steroids, and liver function tests improved subsequently.

The case was followed up and reviewed by Hemoncology team. The origin of the clonal plasma cell infiltrate in liver was possibly attributed to either extramedullary myeloma or post transplant lymphoproliferative disorder (PTLD)/ Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation (IDD-LPDs). However, a negative Epstein Barr virus in-situ hybridization test excluded the possibility of PTLD. The hematological evaluation revealed pancytopenia and Pelger Huet abnormality. Skeletal survey did not reveal any destructive lytic or blastic lesions. She was followed up regularly. Her paraprotein levels continued to rise slowly, almost doubling every two months. The treatment plan included carfilzomib-based induction therapy and dexamethasone to prevent end-organ damage from evolving myeloma. She was also considered for stem cell transplant. In one of the follow ups, the patient presented with acute appendicitis, an appendectomy was performed, but patient passed away in the post-

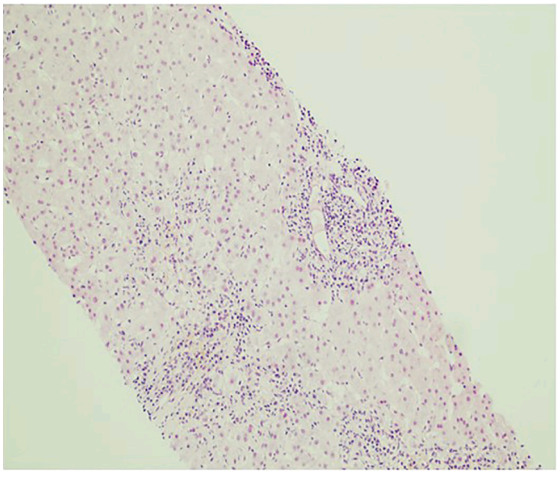

Fig. 1. H&E, X 200**:** The liver core biopsy revealed moderate centrilobular, intra-sinusoidal and portal/periportal inflammatory infiltrate comprised predominantly of plasma cells.

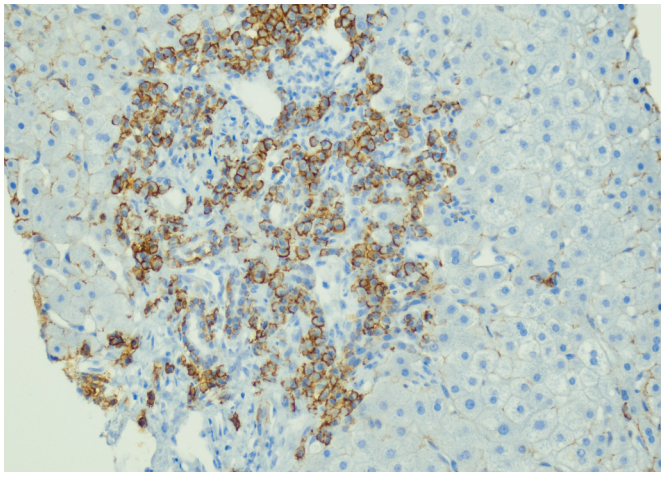

Fig. 2. CD 138, X 400: Immunohistochemical stain for CD138 highlights the plasma cell population.

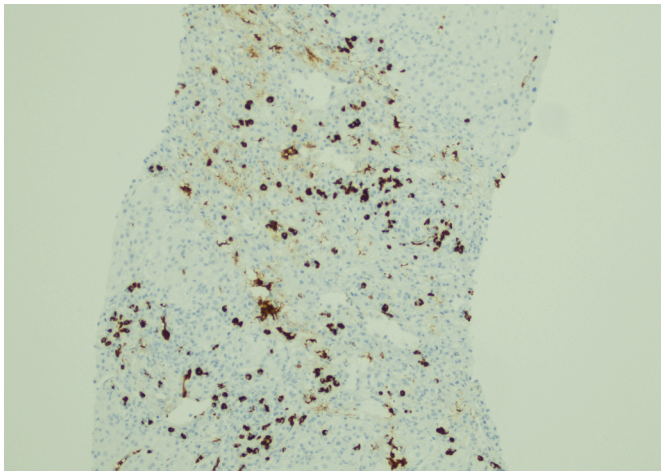

Fig. 3. IgG4, X 400: Immunohistochemical stain for IgG4 highlighted upto 35 plasma cells per high power field at the hot spots in portal tracts.

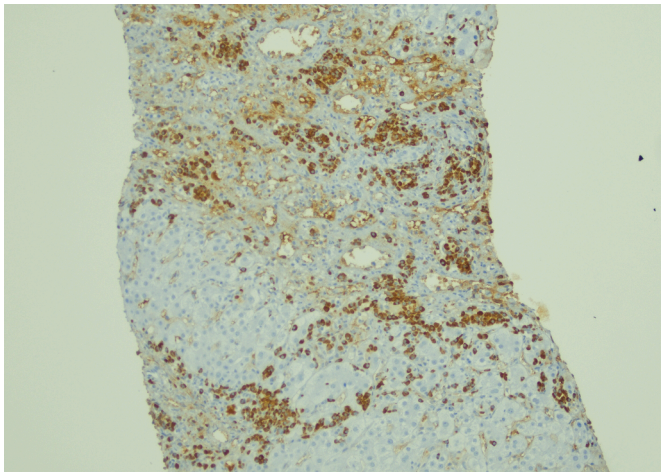

Fig. 4. Kappa, X 400: Immunohistochemical staining reveal atypical kappa, predominant plasma cells (kappa to lambda ratio of 8–10:1).

operative period.

3. Discussion

The present case is the first one in English language medical literature, wherein IgG4 plasma cell dyscrasia is identified in a liver transplant biopsy. The histological features overlapped with late allograft rejection. However, the plasma cell constituents far outweighed the numbers of infiltrating lymphocytes, a distinct contrast from typical acute cellular rejection. Also, the corresponding SPEP was abnormal, thereby prompting evaluation of the clonality of plasma cells. Immunohistochemistry confirmed the kappa restricted nature of the plasma cells, in contrast to polyclonal plasma cell population in previously performed biopsy with late allograft rejection. Clonality analysis for Immunoglobulin heavy and light chain genes rearrangement supported the above interpretation.

Solitary extramedullary plasmacytoma of the liver has been reported previously, although the IgG isotype was not analyzed in those cases [6–12]. A few of the published cases were associated with systemic monoclonal gammopathy. However, liver involvement is relatively rare and usually not the first presentation [10]. In a few of the previous studies, plasma cell neoplasms presenting in the liver have been shown to be associated with plasmablastic morphology. However, the present case did not reveal any plasmablastic cells [1]. The pathogenesis of plasma cell neoplasm in transplant setting is debatable. In this case, the neoplastic clone may have evolved from the plasma cell infiltrate initially presenting as plasma cell rich rejection, which is known to be comprised of a large proportion of IgG4 positive plasma cells [13]. The cytokine and hormonal milieu in the transplant setting along with existing comorbidities may contribute to the clonal evolution of the disease. The complex immunological interactions of donor organ and immunocompromised recipient may also play an important role. On the other hand, the biopsy may be representative of two independent synchronic pathologic processes wherein the liver is colonized and involved by a malignant clone arising in the bone marrow. As bone marrow evaluation was not possible in this case, a precise classification of the lesion as primary extramedullary hepatic plasmacytoma or myeloma with subsequent extramedullary hepatic involvement cannot be made.

The IgG4 plasma cell myeloma cases comprised 4% of all myeloma cases in an original study published in 2013. The prevalence correlated with normal distribution of IgG4 isoform. Clinical course is characterized by disease relapses and exacerbations with fluctuating levels of paraproteins. Correlation with necrotizing fasciitis has been reported wherein the bone marrow infiltrates reveal increased plasma cells but no histologic features pathognomic of IgG4 related disease [1]. The single case of IgG4 myeloma presenting as thyroid mass had concomitant involvement of bone marrow and increased serum levels of $IgG4^3$. The unique biochemical structure of IgG4 limits its ability to form immune complexes or to activate the complement cascade. It also inhibits mast cell degranulation. Consequently, it has a protective role for inflammatory and allergic conditions, but a deleterious role in anti-tumor responses. In IgG4-related disease, serum levels of IgG4 are raised and IgG4 positive polyclonal plasma cell infiltrates are present in tissues. IgG4 positive polyclonal plasma B cell infiltrates are otherwise reported in extrahepatic cholangiocarcinoma, pancreatic carcinoma and malignant melanoma [2,6,14].

4. Conclusion

In conclusion, the presence of plasma cells in a transplant liver may be associated with a plasma cell dyscrasia/neoplasm or myeloma in rare instances. Clinico-pathologic correlation is imperative to draw definitive conclusions. In this case the patient was also diagnosed with plasma cell rich rejection prior to developing the plasma cell neoplasm, which may have impacted evolution of disease. However, additional cases need to be studied in order to understand pathogenesis of plasma cell neoplasms in the transplant setting.

Patient consent

Non-identifiable images, i.e., microphotographs from pathology slides used. Therefore, exemption for patient consent requested.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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