case report

Cold agglutinin disease in fibrolamellar hepatocellular carcinoma: a rare association with a rare cancer variant

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Cold agglutinin disease (CAD) is a rare autoimmune hemolytic anemia. Although it can occur secondary to lymphoproliferative disorders and autoimmune or infectious diseases, CAD is rarely reported as secondary to solid tumors. We report a case of a woman aged 18 years diagnosed with a well-differentiated hepatocellular carcinoma of the fibrolamellar subtype, who was shown to have CAD also. Her general condition, including CAD, improved after targeted therapy with sorafenib for the hepatocellular carcinoma and only conservative measures for the CAD that consisted of avoidance of cold. In summary, although it is an extremely rare association and less common than lymphoproliferative disorders, CAD can be associated with solid tumors.

Cold agglutinin disease (CAD) is a form of autoimmune hemolytic anemia caused by cold-reacting autoantibodies.[1] These autoantibodies, usually of the IgM class, bind to the erythrocyte membrane, leading to premature erythrocyte destruction (hemolysis) that characterizes autoimmune hemolytic anemia.[1] Cold agglutinin disease may be primary (idiopathic) or secondary to lymphoproliferative disorders (LPDs), autoimmune diseases, myeloma, Kaposi sarcoma, angioimmunoblastic lymphoma and infectious conditions, including those caused by *M pneumoniae*, Epstein-Barr virus (EBV), influenza virus, HIV, cytomegalovirus (CMV), rubella, varicella and mumps.[2-4] Only rare cases have been reported to be secondary to solid tumors.[5-6] We report a case of a patient diagnosed to have fibrolamellar hepatocellular carcinoma (FL-HCC) and concomitant CAD.

CASE

A woman aged 18 years presented with right upper quadrant abdominal pain, vomiting, yellowish discoloration of the sclera, dark urine, and weight loss and poor appetite for the previous 3 months. Examination showed pallor, one small (1.0×1.0 cm) left supraclavicular lymph node, right upper quadrant tenderness, and hepatomegaly (liver span, 16 cm). Laboratory investigations showed elevated red cell indices (artifactual); white blood cells, 11.6×10^9/L (normal reference range, $4\text{-}11\times10^9$/L); platelets, 526×10^9/L (reference range, $140\text{-}450\times10^9$/L); erythrocyte sedimentation rate, 150 mm/h (reference range, 0-20); C-reactive protein, 12 mg/L (0-5.99) reticulocytes, 5.4% (0.5-1.5% of RBCs); alanine aminotransferase, 102 U/L; aspartate aminotransferase, 122 U/L; alkaline phosphatase, 187 U/L; total bilirubin, 67.2 mmol/L; direct bilirubin, 7.3 mmol/L; ferritin, 514.3 (g/L; vitamin B12, 1034 pmol/L; and lactate dehydrogenase, 292 U/L; with decreased levels of albumin (28 g/L) and hemoglobin 7.6 g/dL). Blood film examination revealed strong agglutination of RBCs, which is characteristic of CAD. Serum IgA was elevated, while IgG and IgM concentrations were within normal ranges. Negative results were obtained for hepatitis B and C, HIV and EBV (by polymerase chain reaction). *Mycoplasma pneumonia* serology was negative. Alpha-fetoprotein levels were normal. Results of the direct Coombs test and cold agglutinin tests were strongly positive (specific titer not obtained). Chest X-ray was normal. CT abdomen showed a 12×16-cm liver mass with multiple enlarged lymph nodes (**Figure 1**). Liver biopsy showed

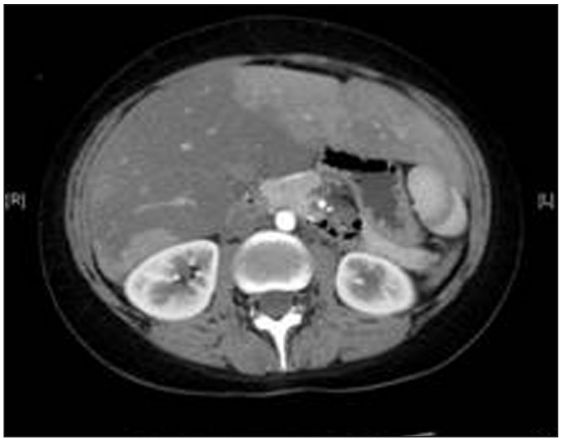

Figure 1. CT scan of abdomen showing the hepatic tumor.

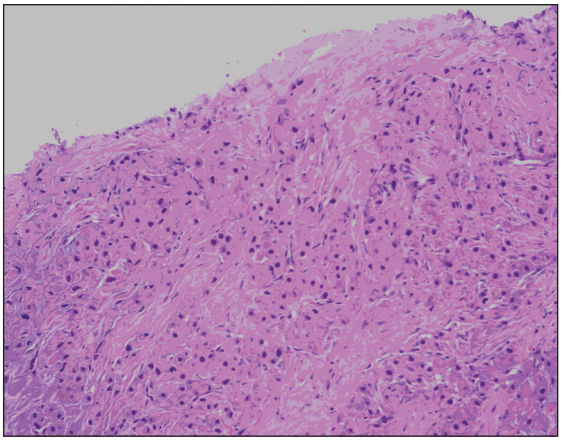

Figure 2b. Liver biopsy showing hepatocellular carcinoma: fibrolamellar subtype (Massionæs trichrome stain ×200).

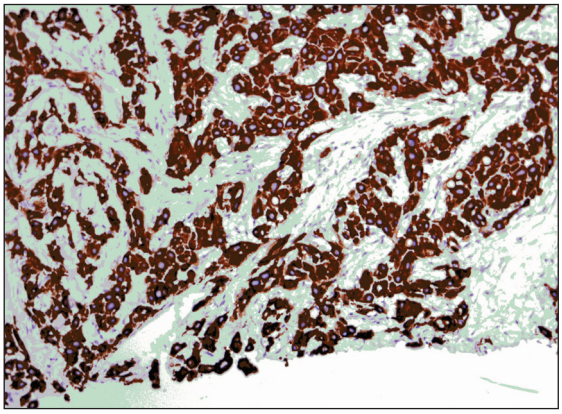

Figure 2a. Liver biopsy showing hepatocellular carcinoma: fibrolamellar subtype (CK stain ×200).

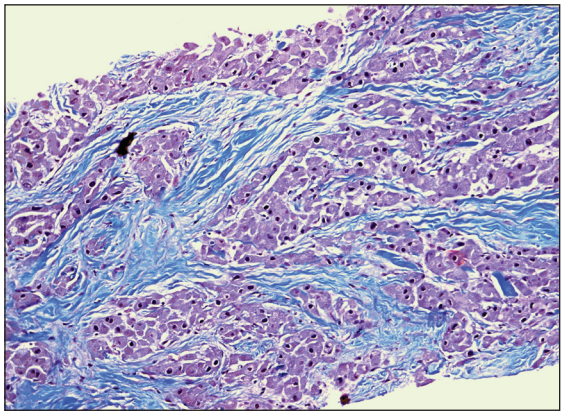

Figure 2c. Liver biopsy showing hepatocellular carcinoma: fibrolamellar subtype (hematoxylin and eosin stain ×200).

a well-differentiated hepatocellular carcinoma of the fibrolamellar subtype (**Figures 2 a, b, c**). Bone marrow aspiration and biopsy results were normal except for erythroid hyperplasia. A lymph node biopsy from the para-aortic lymph node showed total replacement and destruction of architecture by adjacent tumor tissue (local metastasis).

The patient was offered chemotherapy, but the family refused. She was therefore started on targeted therapy with sorafenib 400 mg daily and instructed to avoid exposure to cold. Sorafenib is a multikinase inhibitor of intracellular kinases and receptor tyrosine kinases that decreases cell proliferation and has been found useful in hepatocellular carcinoma (HCC). After 2 months of therapy with sorafenib, the CT abdomen showed mild improvement in the liver mass, and the complete blood count (CBC) and liver function tests were normal. Her blood findings related to CAD disappeared. The patient tolerated the treatment very well. Other treatment would be surgery followed by irradiation to the lymph nodes.

DISCUSSION

FL-HCC is a rare, primary HCC, with one population-based study reporting an age-adjusted incidence rate of 0.02 per 100 000.[7] Although controversial,[7] a recent review by Torbenson[8] supports the unique nature of FL-HCC at clinical, histological and molecular levels. It occurs in young patients without underlying hepatitis, cirrhosis or other risk factors typically associated with HCC.[9] Because of its rarity, little is known about its epidemiology and clinical features,[9] although the recent population-based study of 68 cases[7] in the SEER database between 1986 and 1999 provided data supporting the differences between FL-HCC and HCC. There was a reduced mortality risk of 46% compared with HCC cases, and it was attributed to the lack of underlying liver disease and younger age of patients (mean

and standard deviation, 39 [20] years).[7,8] It may be more common in females than their male HCC counterparts,[7] although a recent review of literature failed to find an association between FL-HCC and gender.[8] Our patient was a young female.

CAD is a rare autoimmune hemolytic anemia. A Norwegian population-based study estimated a prevalence of 16 per million and median age at onset of 67 years.[10] Although most patients display cold-induced circulatory symptoms, enhancing their expression in cold climate, the disease is differentiated from warm agglutinin disease based on antibodies that bind more strongly to red blood cells at 0°C to 4°C.[2,10] More than 90% of cases involve IgM antibodies, which require complement activation and fixation for hemolysis to occur.[11] Antibody thermal amplitude, that is, the highest temperature at which the antibodies bind to antigen, is associated with pathogenicity. Cold-reactive autoantibodies in healthy subjects are usually of no clinical significance because they have low thermal amplitude. If CAD is associated with infections, the resultant anemia usually resolves spontaneously; while antibodies expressed secondary to paraneoplasias or immunocyte neoplasias such as chronic LPDs and lymphomas typically result in chronic disease.[11] When CAD is not associated with other diseases, it is commonly referred to as primary or idiopathic; however, many patients with this form have been found to have an underlying LPD.[12]

Consistent with other reports, our patient had biochemical evidence of hemolysis, including severe anemia, markedly elevated reticulocytes, bilirubin and lactate dehydrogenase.[2,3] Our patient's WBCs were slightly above the upper limit of normal. The CAD diagnosis was suggested by CBC findings (low hemoglobin and artifactually abnormal RBC indices due to agglutination), blood film examination and supported by the positive direct Coombs test and a high-cold agglutinin titer. Our patient, at age 18 years, was younger than typically reported; for example, the youngest of the 86 patients comprising the population-based study by Berentsen et al[10] was aged 30 years. A review by Petz[4] cites two earlier reports where patients had an average age of 66 years and where only 3 of the 21 patients were aged <50 years. Younger patients are usually reported with polyclonal disease occurring in association with viral infections;[1] however, no identifiable viral infection was diagnosed in our patient.

Treatment of CAD can include pharmacotherapy with corticosteroids, immunosuppressive drugs and rituximab, among other agents.[4,12] Such treatments have been successful in some cases; however, varying results have been achieved. Perhaps the most reliable management of CAD is the avoidance of exposure to cold, as was recommended and found to be helpful for our patient. An intuitive question is whether sorafenib therapy itself, or through its regressive effect on FL-HCC, played any role in the disappearance of her CAD findings, which is difficult to answer.

Although the association of CAD with lymphomas is well established, there are a few reports of CAD in patients with other solid tumors. Immunological dysregulation in viral infections and neoplasia has been proposed as a plausible pathogenetic mechanism for similar autoimmune conditions.[5,6] Cao et al[5] reported a case of CAD in a woman aged 65 years with a uterine sarcoma and brain metastasis. The patient was treated with pelvic irradiation for her sarcoma, and with warm transfusion followed by chlorambucil and prednisone for her CAD. Young and Haldane[13] report successful resection of a colorectal tumor in a patient aged 62 years with "long-standing" CAD. The authors emphasize the importance of maintaining core and extremity temperatures during surgery to minimize hemolytic effects of the cold agglutinins. Another recent report[6] described a patient aged 57 years with a 20-year history of hepatitis B who presented with a fever of 2 weeks' duration and was found to have a 5.2-cm liver tumor with a positive diagnosis of CAD. The patient's anemia resolved without treatment following tumor resection. Our finding of CAD in a patient concomitantly diagnosed with hepatocellular carcinoma adds to this scant literature.

In summary, our patient presented with a unique combination of CAD and a rare, solid tumor. She was younger than typical patients with CAD. Her CAD-related problems were successfully managed with avoidance of exposure to cold, and she maintained hemoglobin level of 10 g/dL although her tumor was not yet resolved completely. This unusual co-occurrence indicates that clinicians should be aware of its signs and symptoms to assure that correct diagnosis is made in a timely manner and proper management is offered.

REFERENCES

1. Gertz MA. Cold agglutinin disease. Haematologica 2006;91:439-41.
2. Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. Am J Hematol 2002;69:258-71.
3. Gertz MA. Management of cold haemolytic syndrome. Br J Haematol 2007;138:422-9.
4. Petz LD. Cold antibody autoimmune hemolytic anemias. Blood Rev 2008;22:1-15.
5. Cao L, Kaiser P, Gustin D, Hoffman R, Feldman L. Cold agglutinin disease in a patient with uterine sarcoma. Am J Med Sci 2000;320:352-4.
6. Okada T, Kubota K, Kita J, Kato M, Sawada T. Hepatocellular carcinoma with chronic B-type hepatitis complicated by autoimmune hemolytic anemia: A case report. World J Gastroenterol 2007;13:4401-4.
7. El-Serag HB, Davila JA. Is fibrolamellar carcinoma different from hepatocellular carcinoma? A US population-based study. Hepatology 2004;39:798-803.
8. Torbenson M. Review of the clinicopathologic features of fibrolamellar carcinoma. Adv Anat Pathol 2007;14:217-23.
9. Moreno-Luna LE, Arrieta O, García-Leiva J, Martínez B, Torre A, Uribe M, et al. Clinical and pathologic factors associated with survival in young adult patients with fibrolamellar hepatocarcinoma. BMC Cancer 2005;5:142.
10. Berentsen S, Ulvestad E, Langholm R, Beiske K, Hjorth-Hansen H, Ghanima W, et al. Primary chronic cold agglutinin disease: A population based clinical study of 86 patients. Haematologica 2006;91:460-6.
11. Rosse WF, Hillmen P, Schreiber AD. Immune-mediated hemolytic anemia. Hematol Am Soc Hematol Educ Program 2004:48-62.
12. Berentsen S, Beiske K, Tjønnfjord GE. Primary chronic cold agglutinin disease: An update on pathogenesis, clinical features and therapy. Hematology 2007;12:361-70.
13. Young S, Haldane G. Major colorectal surgery in a patient with cold agglutinin disease. Anesthesia 2006;61:593-6.