



CO-PRESENTATION OF HYPOTHERMIA AND VANISHING BILE DUCT SYNDROME IN HODGKIN'S LYMPHOMA: A CASE REPORT AND A BRIEF REVIEW OF THE LITERATURE

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Abstract – Background: Vanishing bile duct syndrome (VBDS) in association with Hodgkin lymphoma (HL) is well described but not well understood. VBDS is an uncommon form of liver disease manifested by severe cholestasis and progressive liver failure. Specific pathogenesis is largely unknown but several hypothesis have been made, among which paraneoplastic manifestation, direct tumour cells infiltrations and drugs toxicity. Hypothermia is defined as a core body temperature less than 35 degrees C and it is often due to cold exposure and infections (especially caused by Gram-negative bacteria). The synchronous manifestation of both VBDS and severe hypothermia is a very rare condition and we will present a case of a male patient with a diagnosis of HL presenting both VBDS and hypothermia.

Patient Presentation: A 54-year-old male patient, with no history of significant co-morbidities, came to our attention suffering for cervical lymph nodes enlargement. A histologically proven diagnosis of HL lymphocytes-predominant variant was made. The patient presented also jaundice, and the following liver biopsy confirmed the diagnosis of VBDS. He was staged as IIIB (according to Ann Harbor classification) and was treated with ABVD chemotherapy. After the first cycle, the patient suffered for hypothermia, being his body temperature 33°C. He was treated with intravenous fluid replacement and cortisonics and his body temperature grew until the value of 37°C. A few day later, bilirubin value significantly decreased and he was able to sustain the second ABVD cycle, but unfortunately, he died after five days and his death was provoked by hemorrhagic pneumonia.

Results: VBDS is characterized by cholestasis and progressive destruction of the intrahepatic bile ducts (ductopenia). In the literature, various etiologies have been reported to cause ductopenia, with HL being listed as a rare example. How HL causes ductopenia remains ambiguous, and it seems to be related to a paraneoplastic phenomenon causing cytokine release from lymphoma cells. Hypothermia may be fatal if not promptly cured, and in particular, arrhythmia and cardiac arrest represent the major complications. It has been purposed as the causative agent an autonomic neuropathy, with hypothalamus involvement, on a paraneoplastic basis. This is the first case described in the literature of co-presentation of hypothermia and vanishing bile duct syndrome in a patient affected by HL, and as seen, the condition is associated with very poor prognosis and it needs of early detection and cure.



INTRODUCTION

Vanishing bile duct syndrome (VBDS) is a rare disorder characterized by the progressive destruction and disappearance of intra-hepatic bile ducts leading to cholestasis¹. This entity, although rare, has been associated with a variety of benign and malignant conditions². Hypothermia, a core body temperature less than 35 degrees C, is usually due to cold exposure but others causes of hypothermia have been described, such as drugs, metabolic disorders and cancer³. Here we present the first case of hypothermia and VBDS co-presentation in a Hodgkin's lymphoma (HL) affected patient.

CASE REPORT

A 54-year-old male patient, with no history of significant co-morbidities, came to our attention suffering for cervical lymph nodes enlargement, fever, night sweats, weight loss and itch. A biopsy of a left cervical lymph node confirmed the diagnosis of HL, lymphocytes-predominant variant. A computed tomography (CT) scan revealed enlarged cervical, supraclavicular and abdominal lymph nodes, while bone marrow biopsy was negative, establishing a stage IIIB according to Ann Harbor classification.

After the biopsy, the patient was admitted to our Institution for jaundice with tea-colored urine and pale-stools. He denied any use of alcohol and drugs. Liver biochemistry discovered total and direct bilirubin values of 24 mg/dl and 20 mg/dl, respectively; AST 98 U/l; ALT 134 U/l; alkaline phosphatase 558 U/l and gamma-glutamyltransferase 323 U/l. No abnormalities in

liver parenchyma or signs of biliary obstruction were identified by CT scan and cholangio-MRI (Magnetic Resonance). The virology test for hepatitis A virus, hepatitis B virus, hepatitis C virus, HIV and cytomegalovirus were negative. Also, the immunology tests were negative, these included anti-mitochondrial, anti-nuclear, anti-smooth muscle and anti-liver-kidney microsome, and p/c anti-neutrophil cytoplasmatic antibodies. A liver biopsy was performed and the pathologic exam revealed an intrahepatic cholestasis and a lack of bile ducts in more than 50% of portal tracts, without evidence of lymphoma infiltration (Figure 1 show portal tract devoid of the bile duct). During hospitalization, bilirubin and alkaline phosphatase levels increased until values of 51 mg/dl and 766 U/l respectively. Chemotherapy was started employing the scheme: doxorubicin, bleomycin, dacarbazine, and vinblastine (ABVD) given every 14 days. At the start of chemotherapy, the patient suffered for fever (39°C) with bacterial cultures negative. About thirty-six hours after chemotherapy administration, his body temperature decreased until the value of 33°C and the patient presented malaise, profuse transpiration and severe hypotension. A blood sample was taken for specific tests and as result, thyroid function, cortisol level, glucose level were normal, a brain CT scan did not reveal abnormalities. The patient was treated with intravenous fluid replacement and cortisonics and his body temperature grew until the value of 37°C. Ten days after the first cycle of ABVD, bilirubin levels decreased to 29.1 mg/dl (direct bilirubin 28.8 mg/dl) with no further hypothermia symptoms. Unfortunately, the patient died five days after the second cycle of chemotherapy and his death was provoked by hemorrhagic pneumonia.

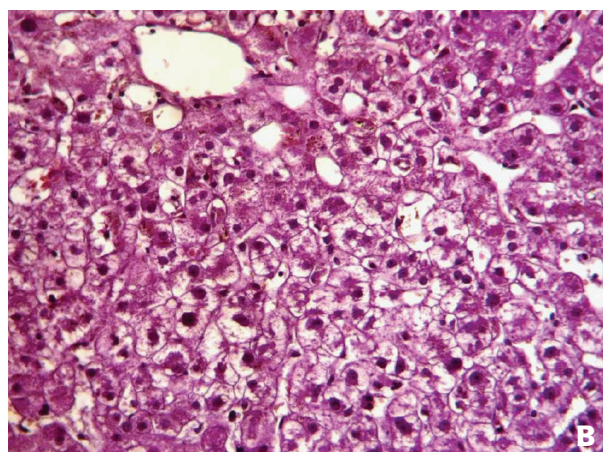
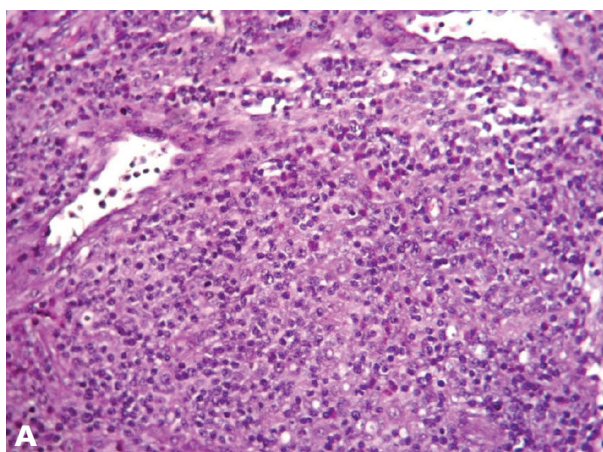


Fig. 1. Hematoxylin and eosin coloration of liver biopsy specimens demonstrating lack of bile ducts without tumor infiltration. Respectively 10 X magnification (A) and 40 X magnification (B).

DISCUSSION

Vanishing bile duct syndrome in Hodgkin's Lymphoma

HL related Jaundice occurs in 3-13% of patients; it is principally due to a hepatic infiltration by lymphoma cells, viral hepatitis and chemotherapy⁴. A rare paraneoplastic syndrome associated to HL, namely VBDS, was first described in 1993 by Hubscher et al⁵. It is histologically defined as a loss of intrahepatic bile ducts in more than 50% of portal tracts without tumor infiltration and other causes of liver disease. This entity, although rare, is not only a HL-associated paraneoplastic syndrome but has been described also in association with drugs, autoimmune disorders, transplantation and infections. The specific mechanism underlying the misbalance between bile ducts cells regeneration and apoptosis are not known. In regard to HL, VBDS seems to be related to a paraneoplastic phenomenon caused by cytokines release by both Reed-Sternberg cells and inflammatory cells infiltrating the tumor. The most common histology associated to VBDS is the "nodular sclerosis", followed by "mixed cellularity" and "lymphocytes depletion", while "lymphocytes predominance", namely the variant found in our patient, is less frequent, and at present, no cases of VBDS has been described in nodular HL patients. HL related VBDS often are seen in young male patients (median age 36,5 years), who present with a palpable neck cervical lymph nodes enlargement; these are characteristics also described in our patient. The eradication of HL appears to be the most significant factor associated with liver function normalization, and this last issue strongly supports the hypothesis that HL may be the direct or indirect cause of the hepatic injury. Nevertheless, the prognosis of VBDS associated to HL is poor with the 80% of death caused by liver failure or sepsis^{6,7}.

Hypothermia in Hodgkin's disease

Hypothermia, defined as a core body temperature less than 35 degrees C (95 F), may be fatal if not promptly cured, and in particular, arrhythmia and cardiac arrest represent the major complications. Hypothermia is most often caused by cold exposure. However, other causes of hypothermia are diabetes, thyroid disorders, severe trauma, drugs, alcohol or paraneoplastic syndromes. HL-associated hypothermia was firstly described in 1981⁸, in a 22-years-old man with Hodgkin's disease infiltrating liver and spleen, who achieved a temperature normalization after combination

chemotherapy. Nowadays, less of twenty cases of HL hypothermia have been described in the literature^{3,9}, and, differently from HL-associated VBDS, hypothermia occurred frequently after chemotherapy. Liver infiltration by lymphoma cells and "mixed cellularity" variant are common characteristics in these patients^{10,11}. Differently from the other cases of HL-associated hypothermia, no liver infiltration by tumour cells was reported in our patient, but the patient had a liver involvement characterized by the loss of intrahepatic ducts without evidence of lymphoma cells infiltration. The occurrence of hypothermia after chemotherapy in patients with liver failure might suggest the liberation of cytokines during the tumor lysis, without an adequate liver catabolism, as a possible pathological mechanism. Moreover, the association between HL-related hypothermia and hypotension has been recurrently described, suggesting an autonomic neuropathy, with hypothalamus involvement, on a paraneoplastic basis as a possible cause of the disorder, on the other hand, occult infiltration of the hypothalamus may be taken into account.

CONCLUSIONS

This is the first case described in the literature of co-presentation of hypothermia and vanishing bile duct syndrome in a patient affected by HL. Both the aforementioned disorders may be considered as paraneoplastic syndromes and they are often markers of aggressive disease, being often associated with poor prognosis. Although rare, their detection may be important for the clinical management and therapeutic decision-making, as well as the detection of the B-symptoms.

CONFLICT OF INTERESTS:

The Authors declare that they have no conflict of interests.

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