Anemia and Hyperbilirubinemia – More Than Just Hemolysis; A Clinicopathologic Case Study

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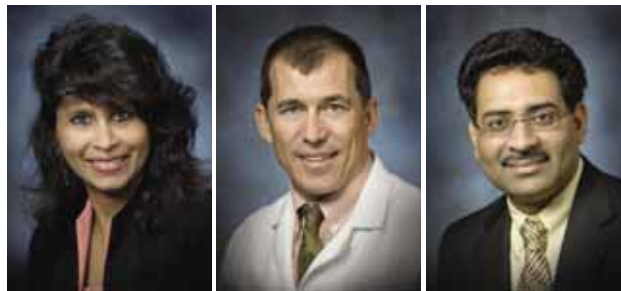*Department of Pathology LGH*

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Admission presentation

A previously healthy 51 year old Caucasian man presented to the emergency room with a 2-month history of a "rash" which initially involved the lower limbs bilaterally, but then gradually progressed to the hands and face. He described it as 2-3 mm slightly raised "red dots" which were not painful or pruritic. It was previously diagnosed as folliculitis, but had not responded to antibiotic treatment.

A week prior to presentation, the patient developed profound and progressive fatigue and weakness, as well as increasing shortness of breath with exertion, resulting in near total confinement to bed. Both legs were markedly swollen and quite painful. There was no active bleeding from the gingiva, nose, gastrointestinal tract, or urinary system, but he complained of dark, foul smelling urine.

His past medical history was significant for chronic back pain controlled with oxycodone. He denied current consumption of alcohol or the use of illicit drugs, although he did admit to a remote history of alcohol and intravenous drug use, more than 20 years ago. His meals consisted mainly of soups from a local supermarket.

On examination, the patient was comfortable in bed but his appearance was disheveled and unwashed with matted hair, multiple piercings in both ears, and a tattoo. His skin and sclerae were icteric. His lower extremities had multiple 2-3 mm palpable purpuric papules and confluent ecchymoses extending from the soles of his feet to the groin (figure 1). A few erythematous papules were also present on the hands and upper chest. Where discrete lesions were identified, they appeared to be folliculocentric (figure 2). Apart from oral thrush and poor dentition, his other systems were unremarkable.

Admission diagnosis

The differential diagnoses considered by the admitting physicians in this patient with purpura/ecchymoses, against a background of icteric skin, were either an autoimmune vasculitis, or hepatitis-induced vasculitis and /or hemolytic anemia.

Laboratory tests

The admission hemoglobin and hematocrit were 6.5 mg/dl and 20.1% respectively , and the total bilirubin was 6.1 (mg/dL). The LDH was normal at 196 (IU/L), as were

Figure 1: Confluent purpura and ecchymoses extending from feet to upper thigh.

Figure 2: Ecchymosis on posterior calf and folliculocentric erythematous macules and papules, medially.

the other liver function tests. A peripheral smear showed hypochromasia , without microcytosis. There was polychromasia and very few spherocytes, but no schiztocytes. The white cell count and platelets were normal, as were the BUN and creatinine. His INR was elevated at 2.2. The urine was positive for urobilinogen. A hematology consultation was requested.

Hematology consultation

The blood smear suggested that there may have been an element of extravascular hemolysis or an episode of bleeding. There was no evidence of bone marrow suppression as evidenced by normal white cell and platelet counts, as well as polychromasia suggesting marrow response to the anemia. It was ultimately felt that the drop in hemoglobin was simply due to hemorrhage into the lower extremities, and the hyperbilirubinemia secondary to reabsorption of the blood. A contributory effect of a nutritional deficiency was also suggested. Red blood cell transfusion was recommended.

Additional Laboratory Tests

The admission haptoglobin level was normal at 80.7 mg/dl (34-225 mg/dL). The factor VII assay was low at 17 (normal 60) and the DIC screen was negative. The Coombs' test, ANA, P-ANCA and C-ANCA were negative. Vitamin B-12, folate, iron, C3 and C4 levels were all within normal range. One day post-admission the total bilirubin was 11.2 mg/dL with a direct component of 6.2 mg/dL. The post-transfusion hemoglobin and hematocrit were 8.3 gm/dL and 25.7%, respectively; however the hemoglobin remained unstable.

Comment

The normal haptoglobin and LDH indicate that hemolysis was a very unlikely cause of the anemia, and also mitigated against the possibility of an autoimmune hemolytic or vasculitic process.

A punch biopsy of the skin was then performed.

Pathology

The 3 mm punch biopsy of the right leg showed a dilated follicular osteum plugged with parakeratotic corneocytes (figure 3). There was associated perifollicular fibrosis and a naked hair shaft underlying the follicular unit. Extravasated erythrocytes and hemosiderin-laden macrophages (highlighted with an iron stain) were present in a perifollicular distribution in a minimally inflammatory background (figure 4). Based on these histologic features a diagnosis of scurvy was rendered.

Follow up

The dermatopathology report prompted evaluation of the level of ascorbic acid, which was markedly reduced to less than 0.12 mg/dL (normal 0.2-1.9 mg/dL), confirming the diagnosis. A daily regimen of 1000mg of oral ascorbic acid was commenced.

On the day after admission, the patient developed right upper quadrant pain and his liver function tests started to rise with a peak LDH, AST and ALT of 643 IU/L, 540 IU/L and 477 IU/L, respectively. The alkaline phosphatase level remained normal. The hepatitis screen was
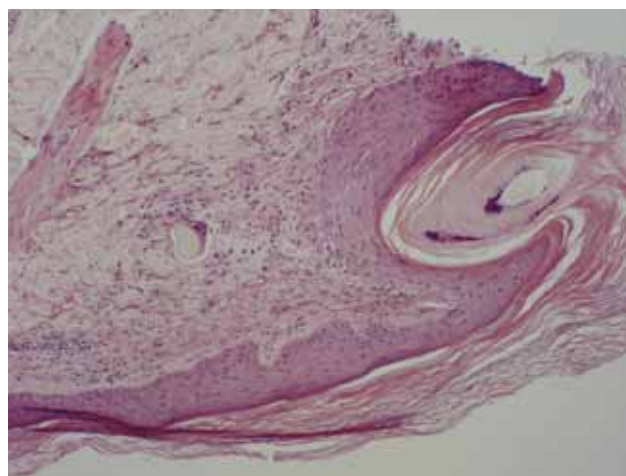

Figure 3: At the edge of the punch biopsy is a dilated follicular osteum plugged with compact and parakeratotic keratin, with an underlying naked hair shaft. Perifollicular extravasated erythrocytes are present (hematoxylin and eosin, original magnification ×100).
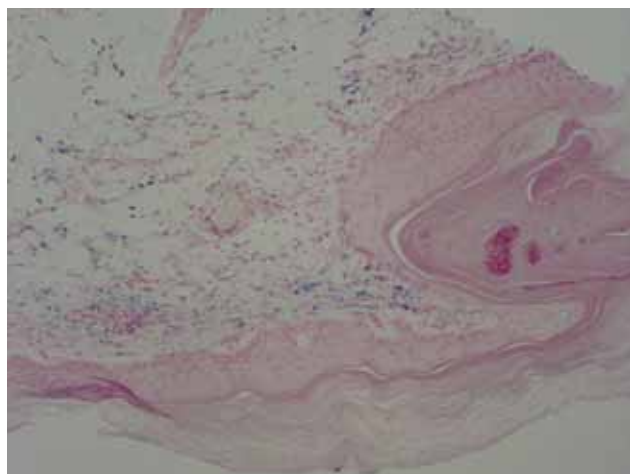
Figure 4: Hemosiderin-laden macrophages and free iron in a perifollicular distribution, highlighted with an iron stain (Perls' iron, original magnification ×100).

positive for hepatitis C. Once the patient's hemodynamic state was stabilized a liver biopsy and cholecystectomy were performed.

Pathology

The liver biopsy showed prominent bilirubinostasis. There were also superimposed changes of chronic hepatitis C with mild activity. This was considerably less lobular activity than is customarily seen in the acute cholestatic phase of hepatitis C, so the degree of cholestasis that was seen was not attributed to hepatitis C, but rather to obstructive cholelithiasis, compounded by the hyperbilirubinemia induced by the resorption of blood.

Follow up and discharge

After vitamin C therapy was started, the patient's hemoglobin stabilized and the bilirubin level dropped. Within 3 days, he acknowledged a dramatic improvement in the appearance of his legs with significant pain relief. He was discharged after 12 days with hemoglobin and hematocrit equal to 10.3 g/dl and 32.7% respectively. He was given 1000 mg daily of vitamin C, and nutritional advice to prevent recurrence of his condition.

DISCUSSION

Scurvy, the clinical syndrome that results from ascorbic acid deficiency, has been recognized for over 3000 years. On long sea-faring voyages, many sailors succumbed to scurvy since only non-perishable foods could be stored on board. On Vasco de Gama's first trip (1497-99) around the Cape of Good Hope, many of his crew developed swelling of the legs, hands, and gums with marked lassitude. Many died, but some recovered after eating oranges. In 1747, the Scottish naval surgeon James Lind demonstrated the efficacy of citrus fruits in the treatment of scurvy-ridden sailors.[1] Starting in 1795 the British navy successfully prevented scurvy by serving lime juice as a regular drink during long sea voyages (thus the nickname "limeys" for British sailors).[2]

Vitamin C is a potent antioxidant that is involved in many oxidation-reduction reactions, but except for its role in collagen synthesis (see below), and its resulting impact on wound healing, the mechanism of action for its various functions is poorly understood.

Ascorbic acid is an organic compound of carbon, hydrogen and oxygen which can be made synthetically from the sugar dextrose. Since humans (and a few other species), lack the enzyme that synthesizes L-ascorbate from glucose, and since ascorbic acid breaks down rapidly when food is processed with heat, we must rely on fresh fruits and vegetables.[3]

Today, scurvy is a relatively uncommon disease and hence the diagnosis may be elusive. Individuals at risk include those who are old, institutionalized, homeless, on dietary fads, alcoholic, chronically ill, or otherwise malnourished.[3,4,5] Studies show that up to 2% of institutionalized psychiatric patients may have vitamin C levels below 0.1 mg/dL.[4] The risk factors in our patient included poor nutrition due to a diet of primarily canned (cooked) soups, and chronic illness, specifically hepatitis C.

The most characteristic clinical finding is perifollicular hemorrhage identified by a hyperkeratotic hair follicle surrounded by a pink halo.[5,6] One of the most commonly described dermatologic findings is "corkscrew" hairs, but this can be easily overlooked if one does not have a heightened suspicion while examining the patient. Additional findings include purpura and ecchymoses especially involving the pretibial area, and poor wound healing. In more severe cases, as in our patient, subcutaneous hemorrhage with woody edema of the legs may result, together with hemarthroses and arthralgias. Conjunctival and gingival hemorrhages with gingival hyperplasia, poor dentition, and subungual splinter hemorrhages can also be seen. A defective immune system predisposes to infections.[2-7]

Anemia is a common presentation, occurring in up to 75% of scorbutic patients.[6] It is due to a combination of

factors related most often to blood loss and suppressed hematopoeisis that result from decreased incorporation of iron and folic acid.[4,6,8] A number of substances in food inhibit absorption of dietary iron, whereas ascorbic acid is one of the most potent enhancers of nonheme absorption of iron because it counteracts the effects of the inhibitors. In addition to increasing the availability of iron for incorporation into hemoglobin,[9] Vitamin C is a co-factor for the conversion of folic acid to its active form, folinic acid.[10]

Rare case reports suggest that hemolysis is a cause of anemia in some patients,[4] but as in our patient, they lack the expected biochemical findings (abnormal haptoglobin and LDH), as well as the peripheral smear stigmata of hemolysis. In other reports, the anemia has been attributed to excessive cutaneous and intramuscular hemorrhage, and it has been postulated that the hyperbilirubinemia is due to resorption of extravasated red blood cells,[5] which was also suggested by the hematologist in the present case.

Due to the generalized poor nutritional state of these patients it is not uncommon for the disease to be compounded by additional deficiencies, such as this patient's coagulopathy, which resulted from a low level of factor VII due to vitamin K deficiency.

Vitamin C is necessary for the hydroxylation of proline and lysine residues during conversion of procollagen into collagen. Vitamin C deficiency causes impaired collagen synthesis which results in defective basement membranes. The resulting loss of vessel wall integrity precipitates extravasation of red cells.[11]

Interestingly, the diagnostic challenge posed by this clinically perplexing patient was resolved through a small punch biopsy. The specimen fortuitously contained a hair follicle at the edge of the biopsy, and when multiple levels through the section were examined, the pathognomonic features of perifollicular hemorrhage and hemosiderosis were recognized. Though follicular hyperkeratosis (figures 3 & 4) was also seen, it is not specific to vitamin C deficiency and can be seen in keratosis pilaris, pityriasis rubra pilaris, icthyosis vulgaris, and vitamin A deficiency. In the last of these entities, the sebaceous glands are also decreased in size.[6] Some ectodermal dysplasia syndromes may also be associated with "corkscrew" hairs.[6]

A clinical cure can result from doses of ascorbic acid as small as 6.5 mg/dL,[12,13] but the recommended dose to induce correction of the deficient state and to rapidly replenish body stores is 100 mg, taken three times a day.[13] Rapid and dramatic improvement with near complete resolution is usually seen within a few weeks. The lassitude, pain and joint symptoms improve within two to three days, while the skin lesions resolve in a few weeks. The "near 100% improvement" acknowledged by this patient three days after commencement of therapy is thus not unusual. Dietary advice is essential for prevention of recurrence in susceptible individuals.

This case highlights the clinical presentation of Scurvy, an uncommon disease of modern times but one which is easily treatable. Failure to diagnose it can result in susceptibility to infections and hemorrhage, with severe debilitation and even eventual demise. Pathology can play an important role in the diagnosis.

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