

# Generalized pruritus as a symptom of hyperferritinemia: A case report and review of the literature

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## Abstract

Generalized pruritus can be the manifestation of many dermatologic and systemic diseases. However, it has been reported infrequently in the literature as a consequence of hyperferritinemia. We report the case of a 70-year-old male presenting to dermatology due to generalized pruritus in the absence of a rash, who was subsequently found to have a significantly elevated serum ferritin and transferrin saturation with otherwise normal iron studies. Hereditary hemochromatosis was ruled out on genetic testing; however, etiologies of secondary iron overload including alcohol use disorder and non-alcoholic fatty liver disease were present. The patient had minimal relief of his pruritus with topical corticosteroids, oral prednisone, and moisturizers. The only successful treatment was phlebotomy which resulted in complete resolution of his long-standing pruritus. We present the fifth case of generalized pruritus associated with hyperferritinemia, treated successfully with phlebotomy.

## Keywords

Pruritus, hyperferritinemia, hemochromatosis

## Introduction

Pruritus is a common presentation to dermatology with a variety of etiologies including dermatologic, systemic, neuropathic, paraneoplastic, and psychogenic causes.<sup>1</sup> We present the case of a 70-year-old male presenting to a dermatology clinic with an 8-month history of pruritus in the absence of a rash. Routine investigations for pruritus surprisingly showed a high ferritin and transferrin saturation, which prompted a workup for hyperferritinemia and hemochromatosis.

## Case report

A 70-year-old man presented with an 8-month history of generalized pruritus that spared the head and face in the absence of a rash. The patient described the pruritus as constant and so severe that it woke him up from sleep. On a 10-point verbal rating score (VRS), he rated the pruritus as 10 (most severe). He denied weight loss, night sweats, or fever and was otherwise well. Medical history included gastroesophageal-reflux

disease (GERD), managed with pantoprazole. Social history was significant for alcohol use disorder and a 50-pack-year history of cigarette smoking. He had quit cigarette smoking 4 years prior to presentation, but actively consumed ~12 alcoholic beverages per week. Family history was negative for both autoimmune and liver disease.

On exam, he did not have any primary skin lesions and no skin pigmentation. There were no burrows seen to suggest scabies. Testing for dermatographism was negative. There was no lymphadenopathy or hepatosplenomegaly and no stigmata of chronic liver disease except for palmar erythema. The patient's body mass index was 25.2.

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Investigations for generalized pruritus were completed including complete blood counts, liver enzymes, C-reactive protein, creatinine, thyroid-stimulating hormone, serum protein electrophoresis, Elisa for BP180 and 230, and ferritin. Investigations were all unremarkable except for the patient's ferritin, which was markedly elevated at 1422 µg/L. This was a surprising result as serum ferritin was ordered to rule out iron deficiency, which is more commonly reported to cause generalized pruritus. Genetic testing for hereditary hemochromatosis was done and revealed a single *HFE* mutation, H63D. Transferrin saturation was found to be elevated at 65%; however, iron and total iron binding capacity were within normal limits. The patient's investigations did not support cholestatic liver disease, chronic liver disease, nor primary biliary cirrhosis; however, a previous abdominal ultrasound had shown evidence of fatty liver. HIV, hepatitis C and B viral testing was negative.

The patient had minimal relief of his pruritus with topical corticosteroids, oral prednisone, and moisturizers. He was advised to decrease his alcohol intake and stop pantoprazole, but no improvement was seen. It was decided that phlebotomy would be initiated at a monthly interval to avoid the complications of chronic iron overload.

Within 24 h of the patient's first phlebotomy, he noted considerable improvement in his pruritus. He further noted that the relief from phlebotomy would last approximately 3 weeks before he would experience breakthrough pruritus prior to his next venesection. He received monthly phlebotomy for 9 months before the interval was lengthened to every 3 months. The patient's ferritin normalized and his pruritus cleared completely. Repeat VRS was 0 (absence of pruritus).

## Discussion

Generalized pruritus as a consequence of iron overload is an uncommon association reported in the literature. To our knowledge, there are only three reports of generalized pruritus as a consequence of hereditary hemochromatosis<sup>2-4</sup> and a single case associated with dysmetabolic hyperferritinemia<sup>5</sup> (Table 1).

The association between hyperferritinemia and pruritus is difficult to establish based on the scarce literature that exists only in the form of case reports.<sup>2-5</sup> Few reviews on hereditary hemochromatosis cite pruritus as a symptom, and those that do reference the case reports discussed above.<sup>7</sup> Interestingly, a survey conducted in 2017 by Haemochromatosis UK looked at the symptomatology among patients with either (a) a diagnosis of hemochromatosis or (b) a genetic mutation for hemochromatosis.<sup>8</sup> Of these patients, 70.4% reported having skin problems, of which 45.3% reported itchiness. Although this

could support the claim of a true association, the itching was not characterized as being generalized versus localized. Furthermore, other reviews of the symptomatology of hemochromatosis did not discuss pruritus as occurring.<sup>9-12</sup>

Our case is a 70-year-old man presenting with generalized pruritus and evidence of hyperferritinemia. He had a single *HFE* mutation, which has not been shown to be a cause of hereditary hemochromatosis nor is it associated with hyperferritinemia in isolation.<sup>13</sup> There is evidence that a single *HFE* mutation in the context of alcoholic liver disease can increase the risk for having excess liver iron stores; however, it does not increase the risk of presenting with increased serum ferritin.<sup>14</sup> The presence of *H63D* in the present case is likely an incidental finding and unrelated to the patient's presentation.

Secondary iron overload results from excess absorption and organic deposition of iron, unrelated to the genetic mutations that cause hereditary hemochromatosis.<sup>13</sup> The most common causes of secondary iron overload include iron-loading anemias such as thalassemia, chronic hemolytic anemias, sickle cell anemia, aplastic anemia, and red blood cell transfusions. Malignancy and chronic inflammatory states can further cause secondary iron overload.<sup>13</sup> The present case demonstrates an unusual case of generalized pruritus as a symptom of iron overload in the context of both alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD).

Alcohol use disorder has been described to lead to an increased serum ferritin and transferrin saturation due to increased intestinal iron absorption, and further decreased levels of hepcidin due to ethanol-induced downregulation of the transcription factor that regulates hepcidin expression.<sup>15,16</sup> Given our patient's history of alcohol use disorder in the absence of chronic liver disease and other causes of secondary iron overload, it is likely a component of the etiology for his hyperferritinemia. NAFLD further can cause secondary iron overload, resulting in increased serum ferritin with normal serum iron as a consequence of hepcidin downregulation from insulin resistance.<sup>17</sup> Our patient had evidence of fatty infiltration in his liver on ultrasound, and an HbA1c in the pre-diabetic range. Fortunately, phlebotomy was very successful, and in fact the only treatment that resolved the patient's pruritus long-term.

The association between hyperferritinemia and generalized pruritus is rarely reported in the literature. However, a complete response to phlebotomy suggests a causal role for the increased iron. A serum ferritin level should be included in the workup for generalized pruritus of unknown cause. We encourage further reports to establish if the association of hyperferritinemia and/or hemochromatosis with generalized pruritus is a true association.

**Table 1.** Review of the literature describing generalized pruritus as a symptom of iron overload.

| Reference                    | Age (years) | Sex | Diagnosis                      | Comorbidities               | Symptoms  | Previously trialed therapies  | Investigations   | Treatment  | Outcome |
|------------------------------|-------------|-----|--------------------------------|-----------------------------|---|---|--|------------|---------|
| Nestler et al. <sup>3</sup>  | 66          | M   | HH                             | Diabetes mellitus           | Generalized pruritus  | Emollients, hydroxyzine   | ↑ Serum iron<br>↑ TS<br>↑ Ferritin<br>Iron deposits on liver biopsy  | Phlebotomy | CR      |
| Hamilton et al. <sup>4</sup> | 70          | F   | HH                             | None                        | Generalized pruritus, ataxia                                      | –   | ↑ ALT<br>↑ Serum iron<br>↑ Ferritin<br>Iron deposits on liver biopsy | Phlebotomy | CR      |
| Kluger et al. <sup>2</sup>   | 47          | F   | HH                             | Osteoarthritis of the hands | Generalized pruritus, weakness, chronic fatigue, 3 kg weight loss | Antihistamines  | ↑ Serum iron<br>↑ Ferritin<br>↑ TS<br>HFE C282Y homozygous           | Phlebotomy | PR      |
| Brigant et al. <sup>5</sup>  | 63          | M   | Dysmetabolic hyperferritinemia | Metabolic syndrome          | Generalized pruritus  | Antihistamines, emollients<br>UVB phototherapy, topical corticosteroids | ↑ TS<br>↑ Ferritin   | Phlebotomy | CR      |
| Osman et al. <sup>6</sup>    | 70          | M   | Secondary iron overload        | Alcohol use disorder, NAFLD | Generalized pruritus  | Topical corticosteroids, systemic corticosteroids, emollients           | ↑ TS<br>↑ Ferritin   | Phlebotomy | CR      |

HH: hereditary hemochromatosis; TS: transferrin saturation; CR: complete resolution; PR: partial resolution; NAFLD: non-alcoholic fatty liver disease; HFE: hemochromatosis; ALT: alanine transaminase; UVB: ultraviolet B.

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### Informed consent

The patient has given consent for publication of this case report.

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