Case Presentation : Hyperferritinemia

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Abstract

Hyperferritinemia is a common finding in clinical practice with many possible causes. Levels above 1000 micrograms per litre can indicate significant underlying pathology, including malignancy; thus, all unexplained hyper ferritinemia require further evaluation. Here, we present a case of a prostate cancer diagnosis in a patient with initial laboratory findings of raised ferritin levels and non-specific symptoms.

Keywords: hyper ferritinemia, underlying pathology

Introduction

Case study.
A 55-year-old Caucasian male was seen in the primary care clinic due to increasing fatigue over the last six months. The medical history, including a systems review, past medical and surgical history, medication history and family history, was unremarkable. He did not smoke, and his alcohol intake was occasional. A general physical examination was also normal. Initial investigations included a complete blood count, haematinics, thyroid profile, renal and liver function tests, haemoglobin A1C, vitamin D levels, coeliac screening and urine analysis. The laboratory results were normal, apart from a raised ferritin level of 1500 micrograms per litre. An electrocardiogram (ECG) and Chest X-RAY were also done, which were normal. Further workup ruled out iron overload and other common conditions associated with raised ferritin but revealed a raised Prostate-specific antigen (PSA). The patient was referred urgently to a urologist. Subsequent Magnetic Resonance Imaging (MRI) of the prostate showed a mass, which was confirmed on biopsy as a high-grade prostate cancer.

Ferritin biochemistry

Ferritin is an iron-storage protein found in cells and blood. Its primary role is to sequester free iron and store it until required by cellular processes. Serum ferritin is a common first-line investigation in anaemia and in patients with non-specific symptoms such as weakness, joint pains, fatigue etc. When low, it is a highly specific marker of depleted body iron stores. However, when it is elevated, many potential causes exist (Table 1). Evidence suggests that raised ferritin levels are frequently overlooked in primary care, with no further follow-up in up to 50% of cases [1].

In approximately 10%, hyper ferritinemia is due to iron overload conditions such as hemochromatosis or congenital anaemias. The remaining 90% are due to other causes, usually secondary to inflammation or cellular damage [2, 3]. Any form of inflammation can raise ferritin levels; hence, it is considered an acute phase reactant. This is because the release of pro-inflammatory mediators stimulate hepcidin synthesis, which facilitates increased gut absorption of iron and ferritin synthesis [2]. In acute conditions, ferritin levels will return to normal once the inflammatory process has resolved. In chronic conditions, ferritin levels tend to persist and may increase further. Persistently raised ferritin is commonly seen in metabolic syndrome, poorly controlled diabetes, alcohol excess, liver disease of any cause and chronic kidney disease [2]. In the absence of the above, raised ferritin, especially if greater than 1000 micrograms per litre, can indicate significant underlying pathology, such as a malignancy [4].

Table 1. Causes of hyperferritinemia [2, 3].

Hyperferritinemia with iron overload	Hemochromatosis Dysmetabolic iron overload syndrome Iatrogenic causes i.e., excess parental iron, blood transfusion Thalassemia
Hyperferritinemia without iron overload	Acute infection/inflammation Excess alcohol intake Metabolic syndrome Diabetes Liver disease of any cause e.g. viral hepatitis, alcoholic liver disease, NAFLD, cirrhosis Autoimmune diseases, e.g. rheumatoid arthritis, Still's disease, Malignancy (haematological and solid tumours)

Discussion

Raised ferritin levels are a common finding and, as mentioned earlier, can be easily overlooked. However, all cases of hyperferritinemia require further evaluation. This should include a thorough medical, social, family (e.g., history of hemochromatosis or congenital anaemia) and occupational history. Recent evidence has shown that prolonged exposure to industrial fumes may also cause hyperferritinemia with iron overload [5]. Repeating serum ferritin levels after a suitable interval is a reasonable strategy if suspecting an acute inflammatory cause or after lifestyle changes, e.g., in persons that drink alcohol, fatty liver disease and metabolic syndrome [6]. An algorithm to investigate unexplained hyperferritinemia is outlined in Figure 1.

This case study highlights underlying malignancy as the cause of hyperferritinemia in our patient. The association between raised ferritin and malignancy has been reported before, with numerous studies showing raised levels in breast, lung, pancreatic, neuroblastoma, glioma, lymphoma and leukaemia [7]. Elevated ferritin levels in malignancy are thought to be secondary to inflammation and cellular damage and not directly related to cancer aetiology. Ferritin may also affect tumour survival by promoting angiogenesis and proliferation [7]. In regards to prostate cancer, elevated ferritin levels were found to be significantly correlated with raised PSA levels in patients with histologically confirmed prostate cancer [8]. Another study showed significantly increased urinary ferritin in patients with prostate cancer compared to BPH and control groups. Based on these findings, the authors proposed that urinary ferritin could be a useful biomarker in prostate cancer [9].

Prostate cancer is the second most common cancer diagnosis in men and the fifth most common cause of cancer death worldwide [10]. The risk factors for developing prostate cancer are non-modifiable and include increasing age and family history. It is more common in men of African Caribbean descent, followed by white men, and is least prevalent in Middle Eastern and Asian men, although incidence is rising in the latter groups [11, 12]. Classically, symptoms associated with prostate cancer are related to the urinary tract and can be split into storage and voiding symptoms, collectively known as lower urinary tract symptoms (LUTS) [11]. However, LUTS are more commonly due to benign prostatic hypertrophy (BPH), which is present in about 50% of men over the age of 50 [13]. Other symptoms associated with prostate cancer include visible haematuria [14] and erectile dysfunction [15]. Prostate cancer can, however, be asymptomatic in early disease or present with non-specific symptoms such as fatigue [16]. Prostate-specific antigen (PSA) levels with age-based cut-offs are routinely used for screening. Unfortunately, the PSA test suffers from a lack of specificity, as it can be elevated for many reasons, including BPH, prostatitis, a urinary tract infection, sexual intercourse, vigorous exercise, and urinary catheterisation [17]. Furthermore, up to 25% of men diagnosed with prostate cancer may have a normal PSA at the time of diagnosis [18]. Performing a digital rectal exam (DRE) can be helpful; an abnormal-feeling prostate was found to be associated with a 43.5 % risk of malignancy [19]. Current NICE guidelines in the UK suggest using age-related PSA cut-offs in conjunction with a DRE in symptomatic men (LUTS) or visible haematuria or erectile dysfunction [20].

Conclusion

A finding of elevated ferritin always requires further evaluation. If unexplained by common causes, rare and potentially more significant causes, including malignancy, must be ruled out, and patients should be referred urgently to secondary care.

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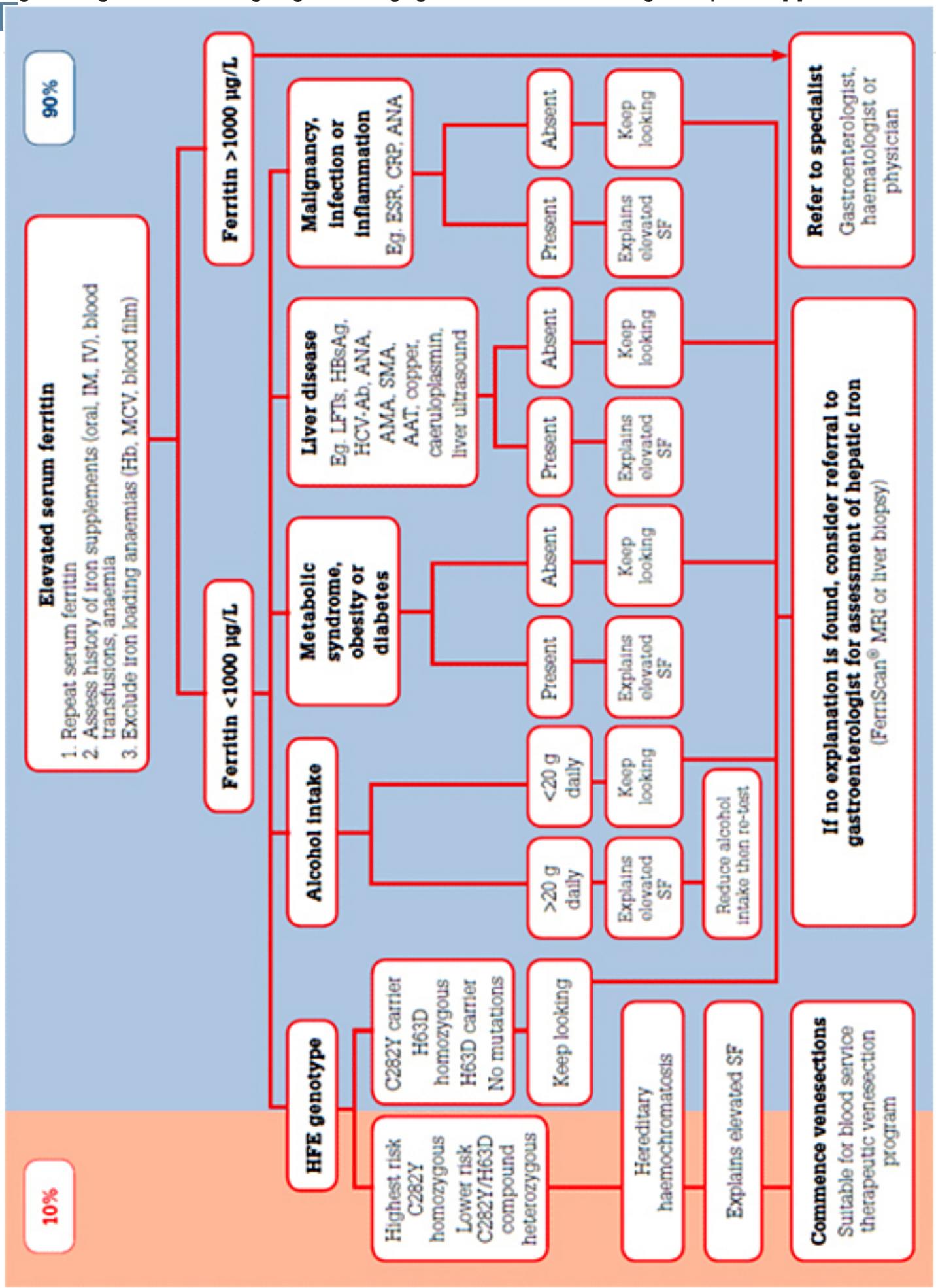
Figure 1. Algorithm for investigating and managing elevated serum ferritin in general practice [3].



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