Urology Case Reports 54 (2024) 102710

Contents lists available at ScienceDirect

Urology Case Reports

journal homepage: www.elsevier.com/locate/eucr

Oncology

Inflammatory myofibroblastic tumor in a patient with X-Linked hypophosphatemia: A case of Occam's razor or Hickam's dictum?

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ARTICLE INFO

Keywords:
Inflammatory myofibroblastic tumor
X-linked hypophosphatemia
Occam's razor
Hickam's dictum

ABSTRACT

We present the case of a patient with X-Linked Hypophosphatemia (XLH) and an inflammatory myofibroblastic tumor (IMT) of the bladder which prompted further investigation into the possible relationship between XLH and IMT i.e. a case of Occam's Razor or Hickam's Dictum?

1. Introduction

X-linked hypophosphatemia (XLH) is a disorder of phosphate wasting and the most common form of heritable rickets arising from loss of function mutations in the gene encoding phosphate-regulating endopeptidase homolog X-linked (PHEX).[1] The clinical presentation most often involves bowing deformities of the legs from softening (osteomalacia) and weakening of the bones and the laboratory findings include low serum phosphorus and low or low normal 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D) levels with normal calcium and 25-hydroxyvitamin D 25(OH)D.[2] The pathophysiology of XLH stems from excess fibroblast growth factor 23 (FGF23), secreted by osteocytes and osteoblasts, that suppresses transcription of genes for sodium phosphate cotransporters in the proximal convoluted tubules of the kidney.[3] These transcriptional changes lead to urinary phosphate wasting and decreased blood phosphorous levels. FGF23 also alters regulation of 1 alpha-hydroxylase that is responsible for synthesis of 1,25-$(OH)_2$D.[1] Given the excess FGF23, a novel treatment approach involves the use of a monoclonal antibody, burosumab, that binds FGF23 to allow production of the sodium phosphate cotransporters and prevent renal phosphorous wasting.[4]

In addition to their role in human metabolic diseases, fibroblast growth factors (FGF) have a role in cancer. For example, FGF19, FGF21, and FGF23 are overexpressed in hepatocellular carcinoma, colon cancer, kidney cancer, and prostate cancer.[5] The mechanism of tumorigenesis is related to the activation of transmembrane tyrosine kinase receptors.[5] As a result, drugs have been developed that target the FGF receptor-mediated signaling cascade in cancers harboring FGF alterations.[6] One example is erdafitinib, a pan-fibroblast growth factor receptor (FGFR) inhibitor for the treatment of locally advanced or metastatic urothelial carcinoma with susceptible FGFR3 or FGFR2 alterations.[6] Similarly, pemigatinib, a small molecule inhibitor of FGFR1, FGFR2 and FGFR3 is FDA-approved for previously treated, locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement.[7] Both erdafinib and pemigatinib inhibit tumor cell proliferation, differentiation and angiogenesis.[6,7]

We present the case of a patient with XLH treated with burosumab who developed an inflammatory myofibroblastic tumor (IMT) of the bladder. IMTs are rare tumors that can arise in a variety of organs including the lung, mesentery, intra-abdominal sites, and upper

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https://doi.org/10.1016/j.eucr.2024.102710
Received 22 February 2024; Accepted 13 March 2024
Available online 13 March 2024

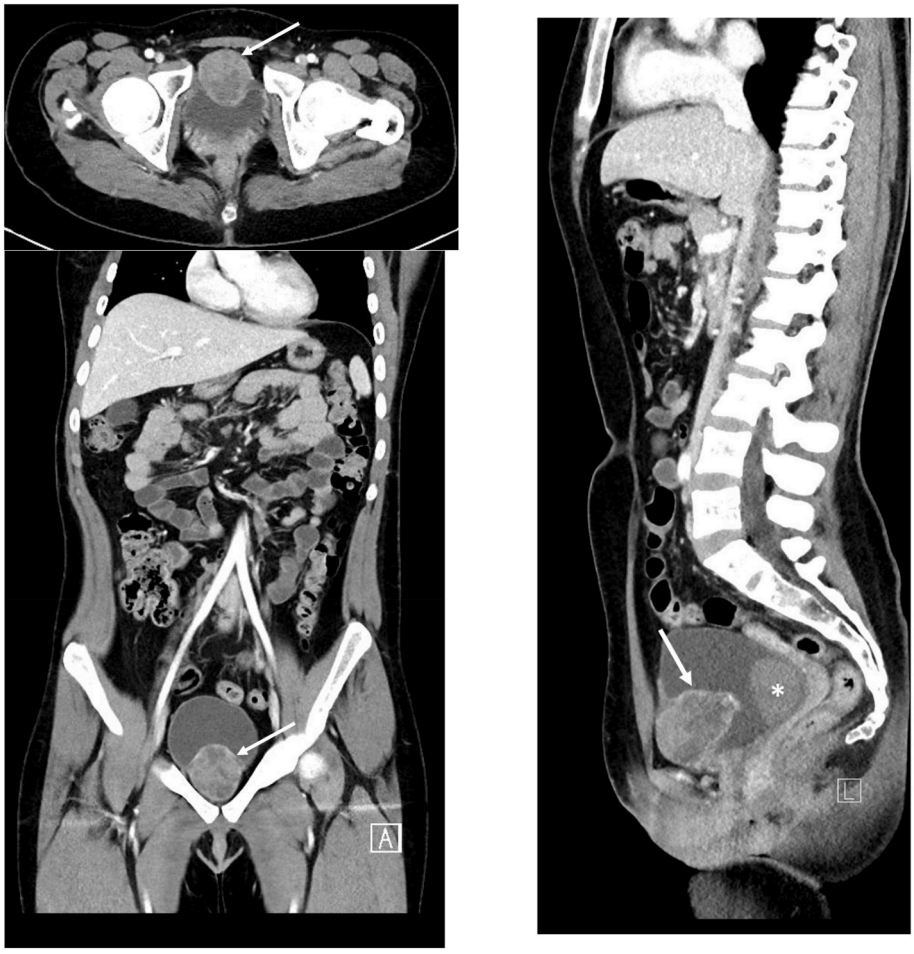

Fig. 1. Transverse, coronal and sagittal contrast enhanced CT images acquired at portal venous phase show heterogeneous solid partially exophytic and partially endophytic mass (white arrow, a-c) arising from the anterior inferior bladder wall. The mass likely shows heterogeneous enhancement on this single phase CT. Additionally, there is layering hematoma along the posterior bladder wall on the sagittal image (asterisk, c).

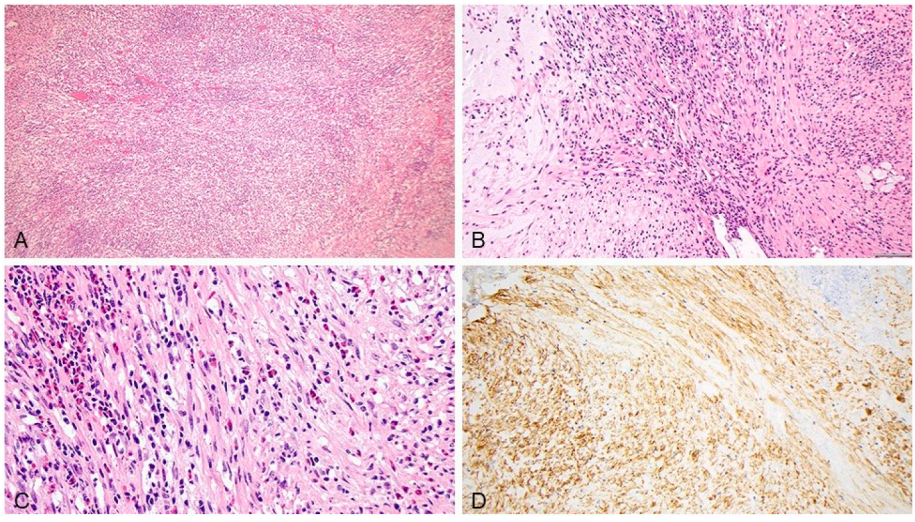

Fig. 2. Histology of inflammatory myofibroblastic tumor (IMT). (A) Low power image of IMT showing variable cellularity and fascicular growth pattern (H&E, 40x). (B) Higher power image of IMT showing hypo- and hypercellular areas and loose arrangements of spindle cells (H&E, 100x). (C) High power image of IMT showing plump myofibroblastic cells with enlarged nuclei and admixed inflammatory cells, primarily eosinophils and plasma cells (H&E, 200x). (D) Tumor shows diffuse cytoplasmic expression of anaplastic lymphoma kinase (ALK) immunohistochemistry (100x).

respiratory tract. IMTs rarely involve the bladder. In general, these tumors have an excellent prognosis with complete surgical resection.[8]

2. Case presentation

A 20 year-old young woman with XLH, complicated by osteomalacia and bilateral bowing of her lower extremities (genua varum) treated with lateral hemiepiphysiodesis, and receiving burosumab therapy, developed gross hematuria over three days and was admitted to the hospital for evaluation. Her history was otherwise significant for episodic hot flashes, increased perspiration and episodes of tachycardia for approximately 1.5 years. A pregnancy test was negative and there was no evidence of a urinary tract infection. A computed tomography (CT) scan of the abdomen and pelvis showed an enhancing 5 cm rounded mass along the anterior inferior bladder wall (Fig. 1). A CT of the chest was unremarkable. Significant laboratory studies included an elevation of total urine metanephrines (710 mcg/g cr [reference range 156–442 mcg/g cr]).

With the patient's young age, the radiologic differential diagnosis for more likely etiologies included mesenchymal tumor, paraganglioma/pheochromocytoma, leiomyoma, hemangioma, and endometriosis. The imaging findings were not specific but were less consistent with urothelial carcinoma or urachal adenocarcinoma (Fig. 1). She was seen by a urologist and scheduled for a cystoscopy with possible transurethral resection of bladder tumor (TURBT) pending further work-up for paraganglioma/pheochromocytoma. Plasma metanephrines, catecholamines and dopamine were within normal limits. Further history suggested that the initial elevation in total urine metanephrines was likely related to adderall and caffeine intake.

The patient underwent a cystoscopy and TURBT revealing a firm, large irregular mass emanating from the anterior bladder wall and extending to the dome of the bladder. Histologic findings demonstrated myofibroblast differentiated spindle cells along with a chronic inflammatory infiltrate,[9,10] consistent with an IMT (Fig. 2). The diagnosis of IMT was confirmed with ALK-1 expression by immunohistochemistry as well as detection of ALK-1 rearrangement by fluorescence *in situ* hybridization (FISH). Given the patient's history of XLH and the potential association of mesenchymal tumors with FGF23 production, *in* situ hybridization (ISH) for FGF23 was performed on the tumor and was negative.[11] One month later the patient underwent a partial cystectomy with negative surgical margins. The patient tolerated the surgery well and no recurrent disease has been identified on subsequent surveillance cystoscopy and pelvic magnetic resonance imaging (MRI).

3. Discussion

When confronting numerous problems within a single patient, different principles may be used to establish a diagnosis. Occam's razor is the principle of parsimony wherein an attempt is made to find a single unifying diagnosis whereas Hickam's dictum suggests that an individual can have many diseases to explain their presentation.[12]

Our case report describes the unusual presentation of an IMT in a young woman with XLH. The development of IMT is unusual given the absence of potential risk factors including advanced age, exposure to carcinogens, indwelling foley catheters, prior bladder augmentation, or exposure to pelvic radiation.[13] With the patient's diagnosis of XLH, it is reasonable to consider a possible relationship between these two uncommon diseases. Phosphaturic mesenchymal tumors secrete FGF23 leading to uncontrolled phosphaturia.[14] There have been phosphaturic mesenchymal tumors identified almost everywhere in the body and the diagnosis is often delayed until years after bone pain, proximal muscle weakness, or isolated hypophosphatemia have developed.[15] To further explore whether there is a potential link between the XLH and IMT, we performed ISH for FGF23 which was negative. As the patient was on a new medication, the FGF23 inhibitor burosumab, we also considered a possible link, however, there have been no reported IMT cases with the use of this novel agent.

This case illustrates the importance of considering the principles of both Occam's razor and Hickam's dictum in patients with different disease processes.

CRediT authorship contribution statement

Farhan Chowdry: Investigation, Writing – original draft, Writing – review & editing. **Kelsey M. Miller:** Investigation, Writing – review & editing. **Ersan Altun:** Investigation, Writing – review & editing. **Sara E. Wobker:** Investigation, Writing – review & editing. **Gary S. Gottesman:** Supervision, Writing – review & editing. **Hikmat Al-Ahmadie:** Investigation, Writing – review & editing. **Tracy L. Rose:** Writing – review & editing. **Eric M. Wallen:** Writing – review & editing. **Matthew I. Milowsky:** Supervision, Writing – original draft, Writing – review & editing.

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