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Case Report

Lower Extremity Pain after Treatment for Inflammatory Myofibroblastic Tumor

Zachary S Berlant*, Rebecca F Carlin

Department of Pediatric Residency Training Program, Columbia University Irving Medical Center, New York, USA

ABSTRACT

Inflammatory myofibroblastic tumors (IMTs) are a rare sarcoma affecting primarily children and young adults. IMTs have the capacity to spread to additional organs, requiring resection, and the treatment may predispose patients to future complications. In this case, a 19-year-old female with a history of IMT requiring extensive abdominal resection presents with severe bilateral hip, knee, and foot pain. She is found to have Subacute Combined Degeneration (SCD) due to deficiencies in all three known vitamin and mineral deficiencies that lead to SCD-Vitamin B12, vitamin E and copper. This is the first case report of a patient with a history of IMT, experiencing SCD. The case will help improve recognition of nutritional deficiencies and optimize care for patients with tumors that have required abdominal organ resection as part of their surgical treatment.

Keywords: Malignant; Inflammatory myofibroblastic tumor; Nutritional deficiencies; Hyperreflexia

INTRODUCTION

Inflammatory Myofibroblastic Tumors (IMTs) are a soft tissue sarcoma of mucosa and mesentery made up of myofibroblasts and immune cells. They are usually a benign tumor in children and young adults, but can grow into important organs. Larger invading tumors require surgical resection as part of their treatment. Micronutrient deficiencies are seen after gastric or pancreatic tumor resection [1,2]. IMTs are rare and heterogenous in the anatomy affected. Micronutrient deficiencies post IMT resection is not well known. Here we present a patient, whose extensive surgical resection treatment for her IMT predisposed her to multiple nutritional deficiencies, resulting in Subacute Combined Degeneration (SCD).

Educational objectives

Understand the signs and symptoms of a nutritional deficiency in patients receiving tumor and intra-abdominal organ resection. Learn to diagnosis and manage subacute combined degeneration in patients at high risk.

CASE PRESENTATION

A 19-year-old female with history of IMT requiring extensive abdominal resection presents with severe bilateral hip, knee and foot pain.

Patient initially presented to the Emergency Department (ED) two weeks prior to presentation after a syncopal event. She recently had SARS-CoV-2 and abnormally heavy menses and was found to have iron deficiency anemia, for which she was admitted and transfused. On discharge she was also scheduled to start outpatient iron infusions for chronic refractory iron deficiency despite oral supplementation. She was then well until five days prior to presentation when she developed dysuria and started Trimethoprim-Sulfamethoxazole (TMP-SMX) for presumed cystitis. She stopped treatment on day three after experiencing altered tongue sensation and taste, tongue swelling, and a dark rash on her lateral lips and cheeks. On the day prior to presentation, she received a ferric carboxymaltose infusion. The patient then presented to the ED overnight after being awoken by severe pain in her hips, knees and feet. Her review of systems is otherwise only remarkable for new onset "tingling" in her bilateral feet and chronic progressive worsening of nighttime vision.

The patient's history is significant for a malignant myofibroblastic tumor of the abdominal cavity managed surgically by resection of the stomach, duodenum, gallbladder, spleen and pancreas 10 years prior. The resection resulted in insulin dependent diabetes and intestinal malabsorption.

On physical exam she has mild tachycardia (109 bpm) but vitals

Correspondence to: Zachary S Berlant, Department of Pediatric Residency Training Program, Columbia University Irving Medical Center, New York, USA, E-mail: zachary.berlant@gmail.com

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are otherwise within normal limits. Musculoskeletal exam reveals significant pain to palpation of the medial hips and knees, exquisitely tender soles of feet, and mild knee swelling without associated erythema or warmth and with full range of motion. She also has extensive, well-healed abdominal scars. The remainder of her exam is unremarkable.

Initial labs demonstrate a normocytic anemia, elevated iron and inflammatory studies and an elevated prothrombin time and international normalized ratio (PT/INR) (Table 1). Imaging reveals normal x-rays of bilateral femurs and hips and no evidence of deep venous thrombosis on doppler of lower extremities.

Table 1: Initial remarkable labs.

Lab index	Lab value	Reference
White blood cell count, (× 10^3/uL)	7.94	3.48-9.42
Hemoglobin, (g/dL)	8.1	11.2-14.7
MCV, (fL)	83.2	79.4-94.7
Red cell diameter Width, %	24.1	11.4-14.7
Platelet count, (10^3/uL)	657	167-774
Activated partial thromboplastin time, (sec)	27.5	23.9-34.7
Prothrombin time, (sec)	17.1	11.9-14.4
International normalization ratio	1.4	0.9-1.1
Creatine kinase, (U/L)	86	40.0-308.0
C-Reactive protein, (mg/L)	0.88	0.00-10.0
Erythrocyte sedimentation rate, (mm/hr)	57	1-20
Iron level, (ug/dL)	596	37-145
Iron binding capacity total, (ug/dL)	709	149-492
Transferrin saturation, %	84	20-50
Ferritin, (ng/mL)	284.6	13.0-150.0

The patient is admitted for pain control and started on ketorolac, acetaminophen, lidocaine patches and morphine without significant relief. Gabapentin and a hydromorphone Patient Controlled Analgesia (PCA) pump are later added resulting in some improvement in both the allodynia and tingling in her feet.

Given improvement with gabapentin, a comprehensive neurological exam to assess for evidence of neuropathies is performed and reveals proprioception deficits in four of 10 toes, absent vibration sensation in the upper thighs bilaterally, and greatly reduced vibration sensation from the hips to the inferior aspect of the knee and in the left forearm.

Vitamin and mineral labs are sent. She is found to be deficient in vitamin B12, vitamin E, vitamin B6, copper, and to have borderline low ceruloplasmin (Table 2).

Table 2: Vitamin and mineral labs.

Lab index	Lab value	Reference
Folate ((Vitamin B9), (ng/mL)	>20.0	≥ 4.8
Vitamin B12, (pg/mL)	188	299-1,054
Homocysteine, (umol/L)	16.6	6.1-15.9
Methylmalonic Acid (umol/L)	0.22	0.00-0.40
Vitamin B1, (nmol/L)	101	70-180
Niacin (Vitamin B3), (ug/mL)	2.17	0.5-8.45
Vitamin B6, (nmol/L)	14.4	20.0-125.0
Vitamin E Alpha-Tocopherol, (mg/L)	<0.5	5.5-18.0
Vitamin E Gamma Tocopherol, (mg/L)	<0.2	0.0-6.0
Copper, (ug/dL)	76.9	80.0-155.0
Ceruloplasmin, (mg/dL)	18	17-54

RESULTS AND DISCUSSION

Differential diagnosis

Our patient has bilateral, symmetric, lower extremity pain that began almost immediately after an iron infusion and responds best to medications for neuropathic pain. The differential includes an iron infusion reaction, SARS-CoV-2 associated peripheral neuropathy, diabetic neuropathy and nutritional deficiency associated neuropathies.

Low-molecular weight iron infusions, such as ferric carboxylmaltose are associated with mild reactions of the complement system occurring in 0.5% of infusions. Symptoms include joint pain, flushing, urticaria, and chest tightness [3]. Iron infusion alone would not explain the constellation of symptoms. SARS-CoV-2 associated paresthesia is not a frequent neurological manifestation and neurologic symptoms usually affect patients with severe acute infection [4]. Diabetic neuropathy can occur in the first 10 years of diagnosis, with incidence rates as high as 23.5%. However, they typically present in a glove and stocking distribution, sparing more proximal nerves, and affect patients with risk factors such as elevated triglycerides, hypertension, history of smoking and cardiovascular disease [5]. Our patient lacks these risk factors and her distribution includes the proximal lower extremities.

Subacute combined degeneration

SCD of the spinal cord occurs when there is loss of the myelinating sheath of the dorsal column. Vitamin B12, vitamin E and copper are essential for the production of myelin around the spinal cord. The lack of myelin affects the dorsal column which is responsible for tactile discrimination, proprioception, and vibration. If the lateral corticospinal tracts are affected it can lead to muscle weakness,

hyperreflexia and spasticity. MRI of the spinal cord shows an inverted V-shaped pattern at the cervical and thoracic level, but is not indicated if there is evidence of deficiency in one of the three nutrients [6]. Vitamin B12 deficiency is the most common etiology of the three and 86% of patients improve after treatment with B12 supplementation. However, only 14% obtain complete resolution. Our patient's anatomy predisposes her to chronic deficiencies in all three nutrients and her recent iron infusion and TMP-SMX course led to an acute increase in vitamin B12 utilization, rapidly dropping her levels.

Vitamin B12 deficiency

The stomach produces glycoproteins haptocorrin and intrinsic factor. Haptocorrin binds vitamin B12 in the stomach and is digested in the duodenum. Intrinsic factor then binds to B12 and the complex of the two is absorbed in the terminal ileum [7]. Our patient's lack of a stomach and duodenum therefore prevents her from absorbing enteral vitamin B12 including the oral supplementation she was taking prior to presentation. For this reason, intramuscular or sublingual supplementation is the preferred method of supplementation and correction of vitamin B12 deficiency in patients with gastric bypasses and Whipple procedures (a proxy for our patient given her post-operative anatomy) [8].

In our patient, there was acutely increased utilization of vitamin B12 as a substrate after her iron infusion. Folate, vitamin B12 and iron are all essential in erythropoiesis with the former two required for purine synthesis and the latter utilized for heme synthesis [7]. The patient's reticulocytosis after the iron infusion is evidence of active erythropoiesis. Her use of TMP-SMX, a folic acid pathway antimetabolite that blocks the conversion of Dihydrofolate (DHF) to Tetrahydrofolate (THF) in purine synthesis, further increased utilization of vitamin B12, which is the cofactor for recycling 5-methyl THF into THF. The methyl trap hypothesis states that in the setting of inadequate vitamin B12, folate is trapped as 5-methyl THF. When TMP-SMX blocks DHF to THF synthesis, there is a theoretical risk of creating additional metabolic demand for vitamin B12 as a cofactor [9].

Vitamin B12 deficiency typically presents with a macrocytic anemia, but in the setting of mixed iron and B12 deficiencies, Mean Corpuscular Volume (MCV) can be normal or decreased and peripheral blood smear erythrocytes can be morphologically normal, as is the case in our patient [10]. Our patient's elevated homocysteine in the setting of high folate levels supports a vitamin B12 deficiency. Clinical manifestations of vitamin B12 deficiency include more than just neuropathy. Given vitamin B12 is necessary for DNA production, deficiency also affects sites undergoing rapid cell division, such as the gastrointestinal tract, which led to our patient's glossitis and altered taste [11].

Vitamin E deficiency

Fat-soluble vitamin absorption occurs predominantly in the duodenum with the help of exocrine pancreatic enzymes. Our patient lacks both the exocrine pancreas and duodenum and her review of systems is consistent with deficiencies of all four fat soluble vitamins. She has nighttime blindness (vitamin A), osteopenia (vitamin D), heavy menses and elevated PT/INR (vitamin K) and dorsal column associated peripheral neuropathies (vitamin E). The earliest sign of vitamin A deficiency manifests as night blindness, with Bitot spots and xeropthalmia being later symptoms [12]. Vitamin K is a cofactor used to produce cofactors II, VII, IX, & X. Clotting factor VII affects the extrinsic pathway, which is measured via PT/INR [13]. Vitamin E deficiency is also associated with spinocerebellar symptoms and ophthalmoplegia, which our patient did not experience [12].

Additional vitamin and mineral deficiencies

Vitamins B1, B3, B6 and copper are also associated with paresthesias. Our patient's low vitamin B6 is likely related to both malabsorption and her oral contraceptive use, which decreases plasma pyridoxal pentophosphates [12].

Final diagnosis

Our patient's vitamin and mineral deficiencies in vitamin B12, vitamin E and copper lead to subacute combined demyelination. SCD is rare in pediatrics as it takes a prolonged exposure to deficiencies to becoming symptomatic. This was a unique case that had deficiencies in all 3 of the nutritional deficiencies that contribute to SCD.

Hospital course

She was given intramuscular vitamin B12 supplementation and was then started on daily sublingual B12 with the plan for further injections as needed. Over the course of her six day admission, her pain resolved with acetaminophen, gabapentin, and morphine. Her vitamin K dose was increased.

Six weeks later, at the time of her next iron infusion, her vitamin B12 was supratherapeutic but she remained deficient in vitamin E and copper, and her gabapentin dose had been weaned. Several hours after the infusion she experienced milder hip, knee, and foot pain that sent her to the ED. Her exam showed no tenderness or neurologic deficits, quickly responded to pain management with two doses of morphine and was discharged without admission. She was started on further supplementation including, vitamins E, B6 and copper.

CONCLUSION

Children and adults with tumors whose resection included intrabdominal organs should be monitored for nutritional related deficiencies due to their increased risk of malabsorption. Vitamin deficiencies should be included in the differential for neuropathic pain. Signs of deficiencies in one or more fat soluble vitamins (nighttime blindness/dry eyes, rickets, easy bleeding and neuropathies), should prompt suspicion for malabsorption. Subacute combined degeneration presents as deficits in the dorsal column (tactile discrimination, proprioception, and vibration) and/or in the lateral corticospinal tracts (muscle weakness, hyperreflexia and spasticity). The differential of vitamin B12, vitamin E and copper deficiencies can be distinguished by lab values. Classic vitamin B12 deficiency is notable for both elevated methylmalonic acid and homocysteine. Copper deficiency will have low copper and ceruloplasmin. However, combined iron and vitamin B12 deficiency can create a false appearance of normocytic anemia. In these cases, peripheral smears can help identify a mixed microcytic and macrocytic presentation.

Our patient presented with SCD due to deficiencies in vitamin B12, vitamin E, and copper that resolved with supplementation. Prompt recognition and treatment of SCD can improve prognosis.

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