CASE OF THE MONTH Sarah Smitherman MD & Robert Lancey MD

A 46 year old white male was admitted from the emergency department with severe pain in his legs, feet and hands, which began two days prior to admission. He described the bilateral pain as shooting and burning in nature; he was writhing in pain and rated its severity as 10/10. He denied trauma, current fever, chills or a history of back pain or arthritis.

The patient reported episodes of this pain since youth and stated that they were worse when he was younger. He also complained of severe fatigue, frequent fevers and an unintentional weight loss of 20 pounds over the past year. He also reported episodic dizziness over the past 20 years which have often been debilitating; these were described as loss of balance, not vertigo. He denied recent chest pain, shortness of breath, nausea, vomiting, hematochezia, melena, constipation or abdominal pain. He reported a history of hearing loss and tinnitus but denied a history of stroke or seizures.

His past medical history includes Meniere's Disease, GERD, CAD (with a stent placed several years ago), LVH on his EKG and chronic, non-healing ulcers on his great toes. Surgery has included cochlear implants for hearing loss and bilateral MTP fusions to aid ulcer healing on his great toes. Medications include gabapentin, amytriptyline and Nexium; he is allergic to IV contrast dye.

Family history is remarkable for a mother with heart disease, TIA and arrhythmias and a maternal grandfather who died of renal failure in his fifties. The patient lives in central Missouri and works as a computer programmer. He denies alcohol abuse or tobacco use.

On admission, vitals revealed T 36.5, P 96, R 22, BP 135/82 and O2 Sat of 98% on RA; pain was rated as 10/10. He was a thin, Caucasian male in significant distress from pain. Cochlear implants were noted. Heart, lung and abdominal exams were normal. Extremity exams revealed no muscular tenderness and no erythema, swelling or tenderness of his joints. Temperature sensation in his legs and feet was significantly impaired; touching the soles of his feet triggered pain that radiated up both legs. Motor strength was 5/5 in all extremities and his cerebellar function was normal. Skin exam revealed multiple punctuate, non-blanching, dark, red and purple papules on his abdomen, hips and fingers.

OK, let's see. This patient is admitted with pain, associated with apparent painful peripheral neuropathy, deafness with cochlear implants, a history of coronary artery disease and a history of chronic pain, dizziness and fatigue. Are these problems related or are there multiple disorders that account for his symptoms? What testing would you order and how would you initially treat the patient?

Admission labs returned WBC 6000, Platelets 221,000, Hgb 13.2 g/dl and Hct 39.2%; the WBC differential was normal. Serum electrolytes were normal, BUN 12, creatinine 0.53 and glucose 93. The LFTs and cardiac enzymes were normal. ESR was 13; CRP was not performed. Urinalysis was normal. The CXR was normal except for tiny nodules in the left upper lobe.

An astute medical student obtained additional family history and found that the patient has multiple family members on his mother's side with kidney disease, heart disease and TIAs. The patient also reported that he has experience these painful crises since early childhood, perhaps as early as 3-4 years of age. Since that time, his symptoms have waxed and waned but, while the pain has generally improved, his hearing loss, dizziness and sensation have worsened. The skin rash has been present since childhood and has gradually spread to more areas. Multiple neurologic workups, including EMGs, have been normal.

Armed with the initial lab data and these additional facts, what is your differential diagnosis? Could it be a genetic disease? Vasculitis? Syphilis? Diabetes? Lupus? (Aren't these disorders always in the differential?) If this is a hereditary disease, what is its linkage? Based upon the family history on his mother's side, perhaps this is an X-linked disorder.

Let's start with this: What is your differential diagnosis for hereditary neuropathies? Charcot-Marie-Tooth, HNPP, muscular dystrophy, others? How about X-linked disorders: Fragile X, McLeod Syndrome, SCID, Sideroblastic Anemia, Duschenne Muscular Dystrophy, Fabry Disease, Hypercalciuria, others?

On subsequent follow up, the patient was diagnosed with Fabry Disease, an X-linked recessive lysosomal storage disease, characterized by a deficiency of alpha-galactosidase A. This leads to an accumulation of globotriaosylceramide or GL-3 in lysosomes of affected tissues. Fabry Disease is caused by a mutation of a gene on Xq22; it occurs in 1 in 55,000 live male births of all ethnicities. As many as 70% of female carriers exhibit symptoms of the disease. The age at diagnosis averages 29 years and the average life span is 50 years with dialysis. An enzyme replacement therapy has been developed which may help to ameliorate end-organ damage in affected patients. Fabrazyme was FDA approved in 2003, costs approximately $250,000 per patient per year and has been shown to clear GSL from capillary endothelium and thereby improve neuropathy, nephropathy and GI symptoms. It is unclear if Fabrazyme decreases the risk for coronary disease or stroke in these patients.

This case illustrates a rare cause of acute pain crisis in adults and reminds us that many patients presenting with acute pain may prove to be educational and, at the same time, pose a diagnostic and therapeutic challenge.

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