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The Limitations of Diagnosis

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Abstract

Extraskeletal Myxoid Chondrosarcoma (EMC) is a rare Soft Tissue Sarcoma (STS) highly correlated with the NR4A3 gene rearrangement. This gene rearrangement has not been found in other tumors. However, its function is not yet fully known in cancer biology. Multiple prospective cohort studies show the population frequency of EMC as approximately 0.0001%. Cases of primary skeletal EMC's have been reported, but the NR4A3 gene rearrangement is less correlated with it as compared to the soft tissue variant. EMC's tend to arise in the soft tissue of the proximal lower extremities and limb girdle in the fifth to sixth decade of life with a male predominance. Cases of EMC arising in the peripheral extremities are rarer still. And pathologic fractures secondary to chondrosarcoma's are also highly unusual. The following patient presents with a primary tumour showing bland histology, arising in an infrequent location and in an atypical age group, primary to an unlikely tissue and associated with a rare presentation. Its only defining characteristic is the NR4A3 gene rearrangement. When does a rare gene rearrangement retain its specificity and serve as sufficient evidence to be diagnostic?

Keywords: Extraskeletal myxoid chondrosarcoma • Talus • NR4A3 gene rearrangement • Soft tissue sarcoma • Diagnosis

Introduction

In the literature of rare cartilaginous tumors a distinction between EMC's arising from the skeleton as opposed to the soft tissues has been insufficiently studied [1-5]. Myxoid Chondrosarcoma's arising from bone are considered either a rare variant of typical chondrosarcoma with myxoid elements, an atypical presentation of an EMC or an altogether unique malignant cartilage tumor. The majority of EMCs show bland immunohistochemistry with only focal or absent staining for typical chondroid markers. But the majority have been shown to have NR4A3 rearrangements [6,7]. As such, it's been suggested as a potential diagnostic marker for EMC. Although no randomized controlled studies have been done to test this hypothesis likely due to the small patient populations available [8].

Case presentation

A 27 years old, African American male with no significant past medical history, seeks medical care for three days of left ankle pain. He denies any method of injury [9,10]. He describes the pain as dull, intermittent and non-radiating. The pain localizes to the anteromedial portions of the ankle. The pain is exacerbated by movement and improved with rest. On examination the left ankle shows an effusion over the anteromedial portion of the medial malleolus which is warm but not erythematous. The ankle is mildly tender to palpation. He retains full range of motion and denies pain with active or passive movement. There are no obvious cuts, bites or sinus tracts suggesting superficial sources of swelling Figure 1. His physical exam is otherwise normal. Due to lack of resources at our outpatient clinic he is referred to the Emergency Department (ED) for an aspiration and further workup [11-14].

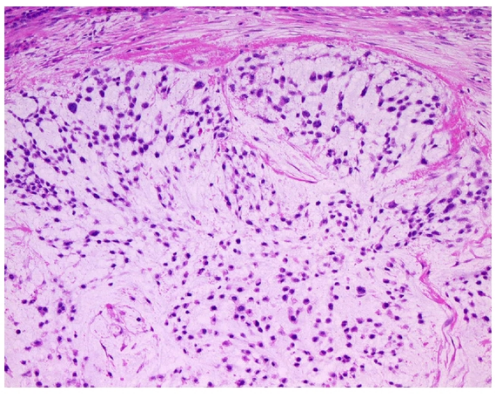

Figure 1. Extraskeletal myxoid chondrosarcoma.

At the ED his L ankle x-ray shows a "subtle relative demineralization of the osseous structure a 3.4 × 2.3 cm lucent lesion in the medial aspect of the talar dome with associated pathologic fracture at the superior aspect of the lesion. No additional lesions are identified. Joint spaces are maintained with diffuse soft tissue swelling throughout the left ankle." MRI with and without contrast

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shows a "large multilobulated, mostly solid enhancing lesion centered within the talus with components extending anterosuperiorly through the talar neck and into the anterior aspect of the tibiotalar joint and posteromedially through the talar body where it encases the flexor digitorum longus and flexor halluces longus tendons, abuts the posterior tibial tendon and compresses the neurovascular structures at the level of the tarsal tunnel."

The patient is placed in a CAM boot and referred to an orthopedic oncologist. Core needle biopsy is performed. Initial pathology suspects chondromyxoid fibroma but pathologist prefaces that if the lesion appears to be more aggressive in the operating room, additional biopsy material will be needed to rule out chondrosarcoma.

Open reduction and internal fixation of the talus is attempted. In the operating room a cavitated talus is visualized *via* posteromedial incision, curetted and removed. The periphery is ablated with electrocautery and peroxide. No extravasation of contrast is noted indicating complete removal of tumor. Autograft with bone marrow aspirate from the right iliac crest is followed by application of multiplane external fixator. The patient is discharged home without complications [15,16].

Surgical pathology shows "chondromyxoid neoplasm with anastomosing cords of mildly atypical histiocytoid cells with reniform nuclei and eosinophilic neoplasm in a myxoid matrix with extravasated blood cells tumor is present at inked surgical margin in an un-oriented specimen." FISH study from send out to Cleveland Clinic shows rearrangement of NR4A3 gene at the t (9q22) locus. Final diagnosis is returned as EMC.

After a patient centered discussion, a limb salvage treatment approach is agreed upon, however patient is informed that the unknown prognosis may lead to a recommendation of amputation in the future. The patient continues close surveillance with the orthopedic oncologist [17,18].

Discussion

EMC's are one of the most rare tumors identified in the literature. Thus information on their prognosis is difficult to come across. Bumpass, in his review of the literature, noted 32 EMC's primary to bone, only 5 which occurred in the foot. Among the studies which have tested EMC's primary to bone for the presence of t (9;22) rearrangement, the frequency has been shown to be much less than its soft tissue counterpart. Antonescu et al. in their clincopathologic comparison of EMC with Skeletal Myxoid Chondrosarcoma's (SMC) showed similar features *via* light microscopy but fundamental differences on the molecular and ultra-structural levels. None of the SMC's they studied had the prototypical NR4A3 gene rearrangement, t (9;22). None arose in the talus. The probability of metastasis was significantly higher (P=0.004) for the EMC group than for the SMC group. However both of these reviews suffer from small sample sizes.

Primary therapy is surgery. It is not clear that radiation therapy adds to surgery for this particular diagnosis, and chemotherapy is not generally used given low response rates in metastatic disease. Limb sparing surgery is standard of care for low grade cartilaginous lesions. No difference in patient survival rates have been shown between an amputation *vs.* limb salvage strategy in STS's of the foot.

Zeytoonjian et al. showed an overall death rate from all STS of 26.6% in contrast to 10.3% for those in the foot and ankle. In Kozawa's retrospective analysis of 31 cases of STS's of the foot and ankle, negative survival prognostic factors included size >5 cm, amputation and need for bone reconstruction. Patients which required more complicated surgery or multiple surgeries, had more perioperative complications.

Conclusion

With rare diseases a physician is increasingly reliant on subjective inference. In the search for specific markers of disease there are multiple disadvantages to potential study designs. These include retrospective observational studies with small sample sizes, genetic markers with low frequency in the population so far tested but not observationally proven through randomized protocols, lack of complete knowledge of the physiology of the marker being used, lack of controls, publication bias, and case matching protocols based off convenience instead of adequate control for confounding variables. These can easily be contaminated by confirmation bias, diagnostic momentum bias, posterior probability errors, and other common logical fallacies. And rareness alone is not sufficient to prove causality. Decision making is also impacted by the connotation of relationships, such as in this case, where the presence of the gene rearrangement turned what was considered a benign tumor into a possible low grade malignant tumor.

When does subjective inference become sufficient to be of diagnostic value? What has to be known to be sure of this subjective relation? When the clinical and radiologic features of a tumor do not correlate with the pathologic and molecular diagnosis, what is the best course of action? Is it better to aggressively treat or use harm-reduction strategies against the unknown? Is it more appropriate to tailor the chosen strategy towards patient preference above all else? Does the search for distinctions in cancer diagnostics blind us to the limitations of evidence? When presented with a diagnostic zebra the tendency to latch on to anything which is distinctive can be alluring but not necessarily specific. Is there a point where definitive diagnosis of a rare entity becomes futile, or even possibly dangerous?

The best treatment course in rare pathologies is a diagnostic dilemma. In the end when faced with uncertainty, the best course of action is to be honest and allow for patient autonomy in healthcare decisions. In this case, using a patient centered approach, the patient and physician agreed that limb salvage was the most desired strategy.

Conflict of Interest

There are none

Ethics statement including patient consent statement-Patient gave written, informed consent for the publication of this case.

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