Case 2 – Anomalous retinal detachment: a case report of infraorbital desmoid fibromatosis

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Abstract
Desmoid tumors, also known as aggressive fibromatosis, are benign, fibrous neoplasms arising from aponeurotic muscle structures of the body. Although they are described as having benign features, these tumors have high tendency to be locally invasive. In some cases where the tumor is attached to an unusual anatomical site such as the head or neck, complete resection is not possible. Therefore, additional treatment such as radiotherapy, hormonal therapy, chemotherapy or noncytotoxic agents may be necessary. We report the case of a 55-year-old man with a desmoid tumor of the left orbital region. The patient presented with retinal detachment, that was initially treated surgical silicone cerclage. A new laser correction was made because of retinal detachment relapse. The appearance of eyelid edema and episodic diplopia resulted in the patient being referred for a computed tomography scan. This revealed the presence of intra-orbital non-homogeneous tissue in the left eye. Local relapse occurred after initial surgical removal and the patient underwent a second surgery. Final pathological examination confirmed a diagnosis of aggressive fibromatosis. Taking into account the site of the neoplasm and the risks related to additional surgery, a chemotherapeutic regimen with vinorelbine and methotrexate was prescribed. Treatment was well tolerated and the orbital mass remained still stable at the last follow-up after 12 months of chemotherapy.

Key words: chemotherapy, desmoid fibromatosis, methotrexate, vinorelbine

Introduction

Desmoid tumors, also known as aggressive fibromatosis, is a fibrous tissue proliferation that arises from the connective tissues of muscle and its overlying fascia [1]. These tumors are rare, accounting for approximately 0.03% of all neoplasms, with the incidence in the general population estimated at 2.4–4.3 new cases per million people each year [2]. Several studies have shown that approximately 37-50% of aggressive fibromatosis arises in the abdominal region and a only a small portion of these are located at extra-abdominal sites, such as the musculature of the shoulder, chest wall, upper arm, thigh and head/neck [3]. Intracranial desmoid tumors are even more rare [4, 5] and, although benign, they can cause significant disability when their growth impacts on surrounding structures. Although desmoid tumors are benign fibroblastic proliferative lesions and lack the ability to metastasize, they can be locally aggressive. Surgery is the traditional management option but is associated with increased recurrence rates.

We report a rare case of desmoid tumor of the orbital region that presented with retinal detachment and, despite its benign nature, relapsed after several surgeries. Taking into account the site of the tumor, the patient was therefore treated with chemotherapy.

Case presentation

A 55-year-old male was admitted to hospital in May 2007 for retinal detachment in the left eye and was treated with surgical silicone cerclage. After about 1 year, retinal detachment relapsed and a second surgery was performed on the same eye where the cerclage was removed and a laser correction was made. In August 2011 the patient developed eyelid edema and episodic diplopia.

A computed tomographic (CT) scan was performed in March 2012 because of worsening of symptoms. The key finding was the presence of a non-homogeneous mass at the level of sub-orbital space of left eye. In April 2012 the patient underwent further surgery to remove the tumor located between the inferior rectus muscle and the inferior oblique muscle; pathological examination docu-

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mented only the presence of inflammatory tissue. In September 2012, 5 months after surgery, the tumor relapsed with a return of diplopia and eyelid edema, without any pain. After a new ophthalmological examination in November 2012, a review of histological specimens was requested. This resulted in a modification of the diagnosis to desmoid fibromatosis, despite the absence of molecular CTNNB1 expression.

The patient presented to our institution in February 2013. Magnetic resonance imaging (MRI) of the facial mass, with and without intravenous contrast medium injection, confirmed the intra-orbital lateral lower left lesion, which measured 23 mm in diameter (Figure 1). Taking into account the site of the tumor, previous surgeries and data on the conservative management of desmoid tumors, a decision was made to spare the eye and not perform any additional surgery. The patient was treated with low-dose chemotherapy with vinorelbine and methotrexate starting in February 2013. A repeat MRI was performed every 3 months after 1 year of chemotherapy treatment. Vinorelbine + methotrexate were well tolerated, diplopia disappeared, and the orbital mass remained stable at the last radiological evaluation in January 2015.

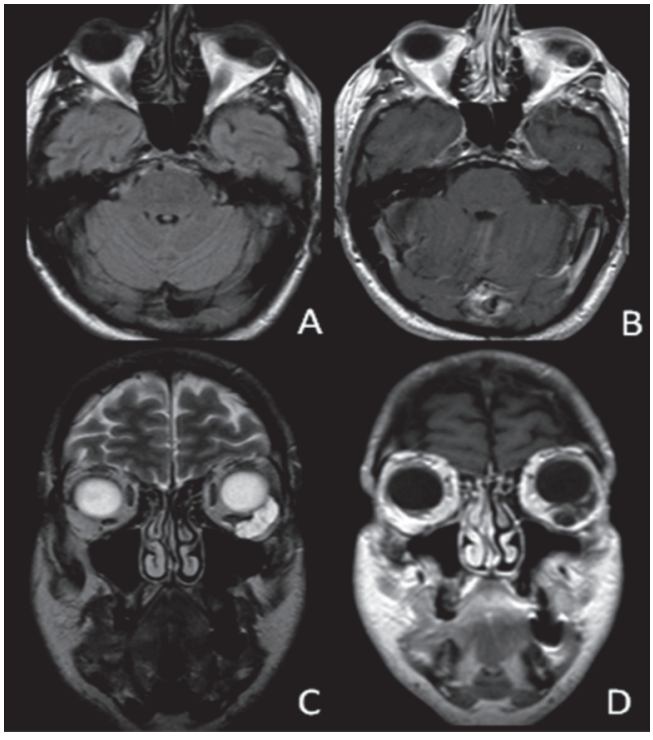

Fig. 1. MRI of the poorly-defined intra-orbital facial mass (Panel A, C) at diagnosis. The lesion, with slight enhancement after gadolinium injection, is strictly contiguous with the inferior rectus muscle, the lateral rectus muscle, and the infero-lateral side of the eyeball (B, D). The mass is stable for dimensional and intensity parameters after contrast medium after 12 months of chemotherapy.

Current management of desmoid tumors

Desmoid tumors are benign locally aggressive slow-growing lesions, also known as aggressive fibromatosis [1], that arise from the aponeurotic muscle structures. They occur generally in young children, although adults may also be affected. The tumors can occur anywhere, but presence in the head and neck region is uncommon (5-10%) [4], and the recurrence rate is high [6, 7].

Current management of desmoid tumors varies but a multidisciplinary approach is required. Given the unpredictable natural course of the lesion, treatment strategies can vary from a "wait and see" policy to surgery and adjuvant therapy. Fiore et al. demonstrated that 50% of patients benefitted from a non-aggressive approach to first-line management [8]. Conversely, it is important to take into account that these lesions can progress to invade local neurovascular structures. In such cases surgery may be necessary, but to achieve negative margins this may need to be quite extensive. Radical surgery is not always possible, especially in head and neck region [9, 10], and in order to achieve local control and reduce the risk of recurrence, adjuvant radiotherapy, chemotherapy, or treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or endocrine therapy (e.g. tamoxifen) may be required [11-13].

In 1989 Weiss and Lackman described a chemotherapeutic regimen combining vincristine and methotrexate on a weekly schedule, which was associated with some initial responses and positive results [14]. Vinorelbine was later substituted for vincristine to decrease the incidence of neurological complications [15]. The French Sarcoma group demonstrated that approximately two-thirds of patients reached disease stabilization or objective response with the combination of vincristine or vinorelbine and methotrexate. Anthracycline regimens demonstrated better objective responses but no difference in progression-free survival, and were associated with side effects unacceptable for the treatment of a benign lesion, including cardiotoxicity and myelosuppression.

The use of pegylated liposomal doxorubicin to treat desmoid tumors has recently been reported by the Sarcoma Unit of the Royal Marsden Hospital, London [16] with an objective response in 33% of patients and stable disease in the other 67%. There has recently been increased interest in the potential role of tyrosine kinase inhibitors in the treatment of extra-abdominal desmoid tumors. In fact, desmoid lesions demonstrate an increased production of PDGF, which may make them suitable for treatment with imatinib. However, clinical data on the use of imatinib in desmoid tumors are not all positive; the French Sarcoma group demonstrated positive initial results but responses at 12

months decreased to 67%. Researchers from Memorial Sloan Kettering have had more positive results with the use of sorafenib, observing a clinical benefit within 2 weeks of treatment initiation in 70% of symptomatic patients [17]. Additional case reports and larger clinical trials are required to better understand and predict the behavior of these tumors, especially in very sensitive locations (e.g. intracranial), with the aim of improving their management.

Conclusion

Aggressive fibromatosis is a rare heterogeneous disease characterized by a variable and often unpredictable clinical course. In this case, desmoid tumor occurred in the orbital region, which is very uncommon. To our knowledge this is one of the first cases of desmoid tumor of the orbital region in an adult. Despite the rarity of this condition in the orbital region, it should be included in the differential diagnosis of ocular disorders. In our case, initial surgery was followed by disease recurrence, with progressively increasing symptoms and infiltration of the orbital region. Both surgery and radiotherapy were not options for this patient and treatment with intravenous vinorelbine and methotrexate was able to stabilize the disease and provide symptom relief. Chemotherapy appears to be a feasible alternative to surgery for desmoid tumors where local tissue infiltration is excessive and surgical excision is not possible.

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Commentary

The case of an orbital desmoid tumor (DT) presented by Dr. B. Vincenzi and colleagues illustrates the heterogeneity and ubiquity of this entity. As the authors mentioned, the head and neck is a rare location for DT, representing <5% of cases. Moreover, most head and neck DTs are located in neck region, with only 4% in the orbital space [1]. Given that the case highlights an exceptional site for DT, there is no existing data on critical issues, including clinical impact and the effectiveness of different therapeutic options.

Sporadic DT shows nuclear immunoreactivity for β-catenin in around 88% of cases and usually these cases include somatic mutations involving exon 3 of CTNNB1 gene [2]. In the reported case, no β-catenin protein expression was demonstrated meaning that the diagnosis had to be based on the similarity of tumor features to other DTs. Low-grade myofibrosarcoma, solitary fibrous tumor or low-

grade fibromyxoid sarcoma are all tumors that have some similarities to DT [3]. The other entity that perhaps should be taken into account in this specific location is orbital pseudotumor, also known as idiopathic orbital inflammation. The histology of the tumor in the current case therefore needs to be clearly described due to the rarity of tumor location and the unusual negativity for nuclear β-catenin immunostaining or CTNNB1 gene mutation.

Radiologically, the retro-orbital lesion appears as an ill-defined mass in T1-weighted MRI images. Typically, DT shows a homogeneous isointense mass on T1-weighted images and bands of low signal intensity can be observed within the tumor. In the case presented here, the lesion seems hypointense with respect to muscle in T1-weighted sequence and this may be also in accordance with DT. On the other hand, low signal bands seem to be evident in all sequences. Thus, although the images are not entirely characteristic of DT they could be considered compatible with this diagnosis [4].

Regarding tumor management in this patient, surgery was first performed in April 2012. It is likely that the aim of surgery was to both resolve diplopia and to obtain histological samples to assist in making a pathologic diagnosis. Currently, surgery is not recommended as first-line therapy for DT and should be avoided in most cases, except for those with rapidly progressive disease [5]. I agree with authors that further surgery was inappropriate in this patient and would have had devastating effects on the affected eye. Avoidance of radiotherapy also seems like a judicious decision. Apart from proton beam therapy, other radiation therapy modalities would be highly likely to result in vision loss [6].

Systemic therapy with vinorelbine and methotrexate showed clinical benefit by relief of with diplopia. Other systemic options, such as hormonal therapy (tamoxifen or raloxifene) or cyclo-oxygenase-2 (COX-2) inhibitors (sulindac or indomethacin), have been recommended in DT. However, the response rate varies widely and there is a lack of consensus about issues such as the dose of tamoxifen. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to have clinical activity but majority of responders experienced a delayed response with a mean time of 24 months [7]. Weekly administration of low doses of vinka alkaloids and methotrexate is the most frequently used chemotherapy combination for the treatment of DT. In general, stabilization and partial response rates of 60% and 40%, respectively, have been obtained [8]. As was seen in the current case, symptomatic relief is often achieved in the absence of tumor shrinkage after chemotherapy administration in DT.

In conclusion, the case illustrates a highly unusual clinical location of DT. Local recurrence was treated with vinorelbine and methotrexate obtaining clinical benefit and eye preservation. The case highlights the need for a multidisciplinary and consultative approach to DT management.

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