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CASE REPORT

Novel use of propranolol for management of pain in children with vertebral hemangioma: report of two cases

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Abstract
Introduction Vertebral hemangioma (VH) is an exceedingly rare neoplasm in pediatric population with less than 10 cases reported in the literature. It is usually asymptomatic in adults and diagnosed incidentally at radiographic investigations of other medical conditions. In this report, we describe two children who presented to our institution with severe back pain and were diagnosed with VH.
Case reports Case 1 was an 8-year-old male with a pain score of 10 out of 10 at presentation. Clinical investigations eliminated the possibility of a neoplasm or infectious process and MRI findings were highly suggestive of an aggressive vertebral hemangioma. Case 2 was a 17-year-old female who presented with back pain radiating to shoulders. Her pain score was 4 out of 10 and she was diagnosed with vertebral hemangioma due to the specific findings on MRI studies.
Discussion Both patients received propranolol with a dose of 20 and 40 mg per day, respectively. They were free of pain at 2 months follow-up. There are different invasive treatment modalities for the management of VH, including vertebroplasty, kyphoplasty, radiotherapy, alcohol injection, embolization, and surgery. These methods have been used in adult patients for several years, but each of them has potential risks which make these options unsuitable for children.
Conclusion Propranolol is a beta blocker which is safely used in the management of infantile hemangiomas. This is the first report demonstrating its efficacy in symptomatic treatment of childhood VH. The lesions did not show any regression, but the pain relief obtained was very significant under propranolol therapy.

Keywords Vertebral hemangioma · Propranolol · Pain · Management · Aggressive · Pediatric

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Introduction

Hemangioma is the most commonly observed benign tumor of the vertebral column in adults. Estimated incidence is 10–12 % on large autopsy series and review of plain films indicated a slight female predilection [11, 26]. Its incidence peaks between the third and fifth decades [16] with thoracic and lumbar spine being most commonly involved. They usually present as incidental lesions on radiographs without causing any symptoms [11]. Occasionally, they may become symptomatic causing pain and neurologic deficits. Moreover, vertebral hemangiomas located at midthoracic region are more likely to cause pain due to the small diameter of the vertebral canal at that region [3]. Diagnosis is made by the radiologic appearance with or without histologic examination [10].

Vertebral hemangiomas (VH) are extremely rare in pediatric age group in contrast to the cutaneous hemangiomas which are commonly observed in infants. Back pain is an important clinical manifestation in children and the possibility of finding an underlying pathology is high [17]. Among the vast number

of diseases included in differential diagnosis, VH is one of the least likely diagnoses. However, treatment of symptomatic vertebral hemangioma (SVH) is far more difficult in children when compared to adults.

There are several treatment modalities for controlling pain in adult patients with VH including analgesics, vertebroplasty, kyphoplasty, radiotherapy, intralesional alcohol injection, transarterial embolization, and, in some cases, surgery. Some of these methods have also been used in a low number of pediatric cases [2, 5, 6, 9, 15, 19, 24, 32]. However, these treatment options almost always come with potential risks that cannot often be taken in children. We used propranolol, which is the first-line drug for management of infantile hemangiomas, and we were able to observe very favorable response with complete pain relief in two cases. To the best of our knowledge, this is the first report demonstrating the effect of propranolol in symptomatic treatment of vertebral hemangiomas. In this study, we discuss propranolol and other treatment options for pain control in VH and their possible complications.

Case reports

Case 1

An 8-year-old boy presented to our clinic with a 1.5 year history of severe back pain. He has been under medical care in an outside center throughout this time. He was prescribed nonsteroidal anti-inflammatory drugs, but his pain did not ease despite taking 24 tablets per day and reported pain score was 10/10. Family history and past medical history were otherwise unremarkable. Physical examination did not reveal any neurologic deficits. Laboratory investigations showed slight normocytic anemia with low Hb (11.2 g/dL; normal range, 11.5–15.5 g/dL) and normal MCV (81 fL; normal range, 77–92 fL). Magnetic resonance imaging (MRI) of thoracic spine showed low signal intensity at T1-weighted images and high intensity at T2-weighted images of T5 vertebral body along with linear striations. Significant vertebral body height loss, bulging of posterior cortex indicated an aggressive behavior. There was no cortical destruction, accompanying soft tissue intensity or spinal cord compression (Fig. 1a and b). A wide spectrum of diseases was considered in differential diagnosis including infectious processes, metastatic tumors, Langerhans cell histiocytosis, osteoid osteoma, and lymphoma. Biopsy was performed to make a definitive diagnosis, however, it was not diagnostic. Due to the potential complications and risk of a new biopsy attempt, his family did not give informed consent for further interventions. Review of all systems, blood tests, PET-computed tomography (CT) scan and whole-body bone scintigraphy failed to identify any malignancy. Based on the available clinical history and results of investigations, he was diagnosed with aggressive hemangioma and non-invasive treatment options were discussed with the family. Oral steroid treatment with 40 mg prednisolone/m^3/day was given for 1 month, but did not relieve his intense pain. Then, propranolol which is commonly used for patients with infantile hemangioma was given to the patient at a dose of 20 mg/day (1 mg/kg/day). The patient was closely monitored for response to therapy and for potential side effects. His pain levels decreased gradually, and all analgesics were discontinued. After 2 months of propranolol therapy, his pain level was 0/10. At 18 months of propranolol treatment, the size of the lesion on repeated MRI scan did not show any regression (Fig. 1c and d); however, the patient remained free of pain.

Case 2

A 17-year-old girl was admitted to our hospital with back pain radiating to shoulders and rated her pain as 4/10. Past medical history and laboratory analysis were unremarkable. Thoracic spine MRI revealed punctuate areas with high signal intensity on T1- and T2-weighted images in a background of high intensity areas, equivalent to “polka dot” appearance on CT scans (Fig. 2a and b). These specific findings were highly suggestive of vertebral hemangioma and based on our experience from the previous patient, we decided to control her pain with propranolol at a dose of 40 mg/day (maximal dose for children). The patient responded dramatically and she was free of pain at 2 months of propranolol therapy. On repeated MRI scan after 6 months of therapy, there was no change in dimensions and radiographic features of the lesion (Fig. 2d, e and f).

Discussion

Pain is the main presenting symptom in cases with aggressive vertebral hemangioma, as experienced by up to 54 % of patients with SVH [16]. The pathogenesis of pain includes direct neural compression caused by extension or bleeding of tumor into extradural space, expansion of the involved vertebra, compression fractures, and the stealing of blood by tumor leading to ischemia of spinal cord [33]. Oral analgesics are the first-line drugs used for the management of pain in VH. Despite the diversity of treatment options, currently, there is no consensus about the optimal treatment modality for analgesic-resistant adult and pediatric cases.

Vertebroplasty is a technique that involves the injection of an acrylic material, polymethylmethacrylate (PMMA), into the involved vertebral body and polymerization of injected cement causes a permenant sclerosis of hemangiomatous vessels [14]. It has several advantages as a

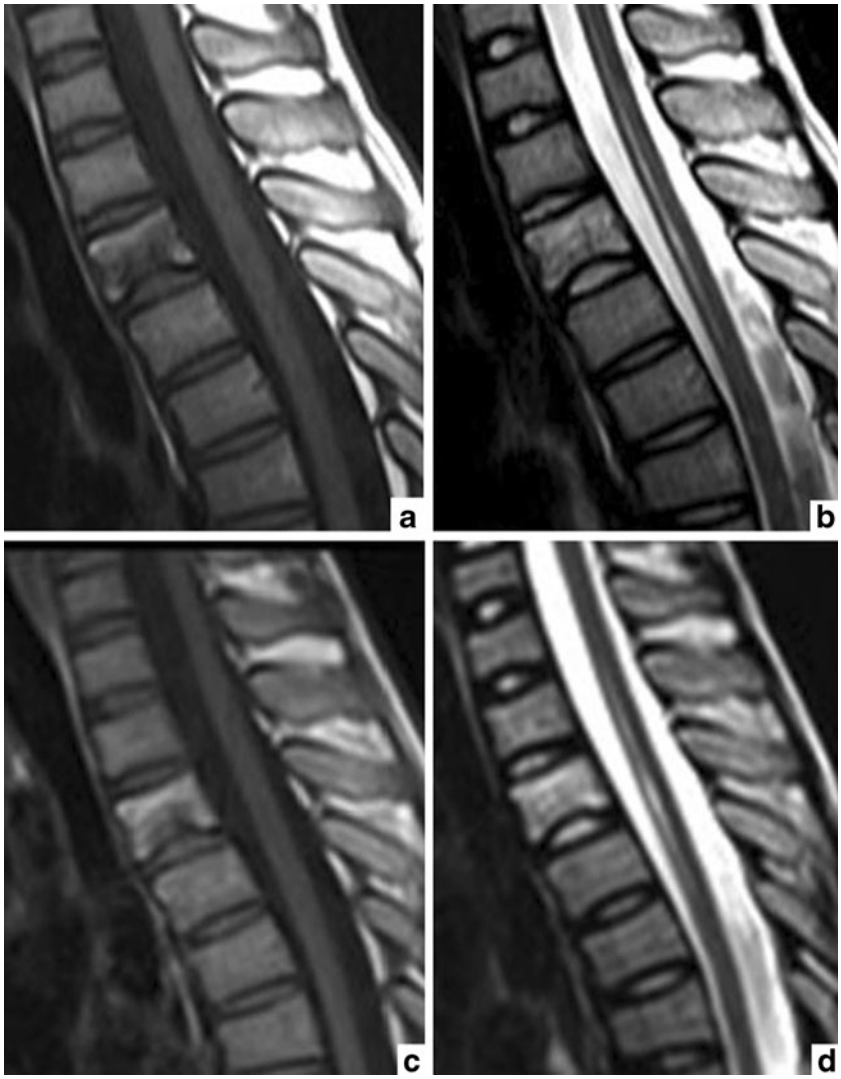

Fig. 1 Sagittal T1- (**a**) and T2-weighted (**b**) MRI images of case 1 demonstrating a hemangioma of the fifth thoracic vertebra which is hypointense on T1W section and hyperintense on T2W image with height loss and vertical striations. After 1 year of propranolol treatment, sagittal T1WI (**c**) and T2WI (**d**) showed no change in the characteristics and dimensions of the lesion

minimally invasive approach with early pain resolution, low rate of complications, and long-term recovery [14, 35]. The success rate for this technique was 80–100 % in different studies [8, 14, 23]. On the other hand, it has several complications, mostly due to the cement use including leakage, cement embolism, and local or systemic reactions against cement [22]. Cement leakage into the spinal canal or neural foramina, which is the most frequent complication of the procedure, may cause neurological deficits requiring surgical intervention. Kyphoplasty has similarities to VP. It involves inflation of a balloon inside the affected vertebral body to create a low pressure cavity and then filling this cavity with PMMA or calcium phosphate. In contrast to VP, it maintains the original height of the involved vertebra [23]. Complications of kyphoplasty are similar to VP, but the risk of cement leakage is low due to the predetermination of the volume of cement incorporated according to the volume of inflated balloon [23].

Hemangiomas are radiosensitive tumors and a radiation dose of 30–40 Gy is sufficient for significant pain relief [16]. It shows its effects through endothelial cell damage with elimination of abnormal vessels [16]. Bone necrosis, growth arrest, skin ulceration, and malignancy are among the side effects of radiation therapy. It is recommended only as an adjuvant therapy following subtotal excision of the tumor in order to prevent recurrences [3]. In their clinical study with 63 patients, Heyd et al. reported complete remission in only 57 % of their cases [16]. However, due to their higher rates of mitosis and cell turnover, children are more susceptible to the acute and late toxicity of radiation. Therefore, radiotherapy appears to be least favorable treatment option for management of pain in pediatric era.

Alcohol injection is another treatment option for symptomatic VH and results are satisfactory with a success rate of 86 % in one study [13, 29]. Injected alcohol causes sclerosis and subsequent shrinkage of the hemangioma due to the endothelial damage and thrombosis of vessels. However there are many risks associated with alcohol injection including Brown–Sequard syndrome, pathologic fractures, hemodynamic instabilities [28, 34], and recurrence of tumor.

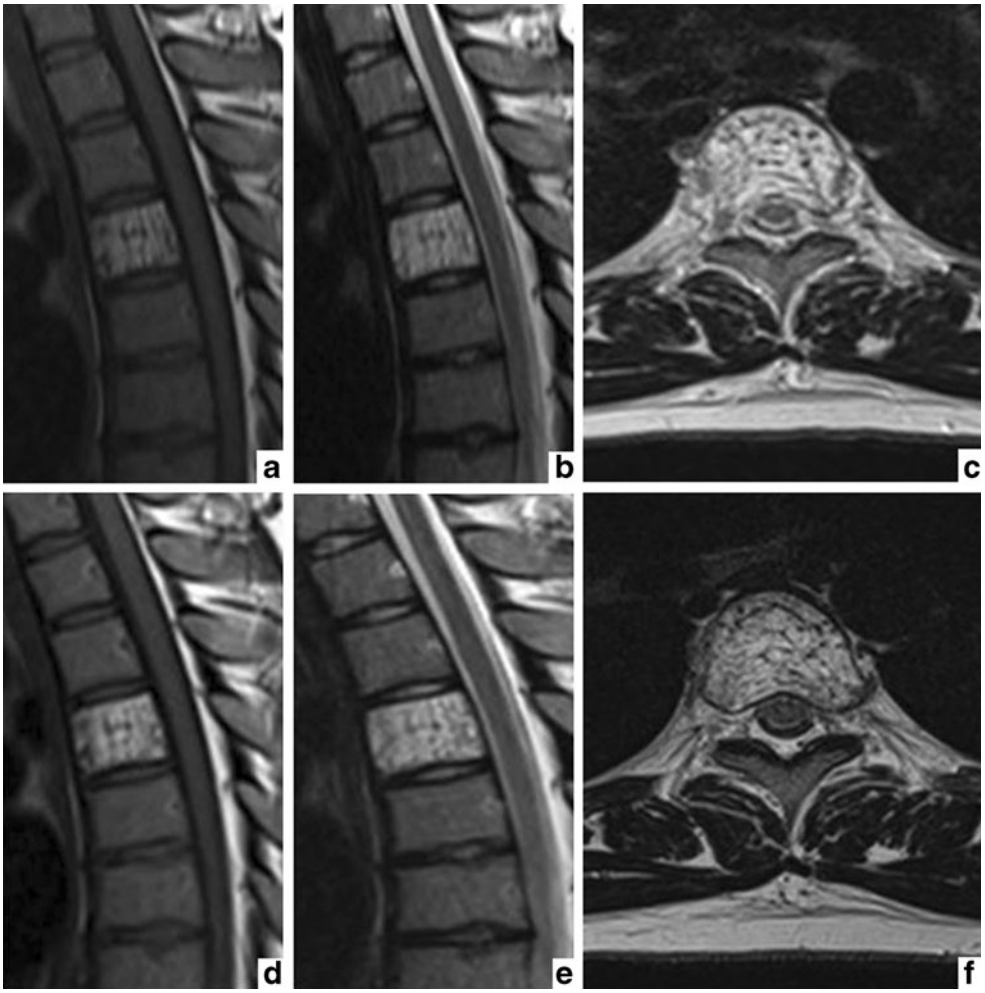

Fig. 2 Sagittal T1- (**a**) and T2-weigted (**b**) MRI sections showing a hemangioma of the fourth thoracic vertebra which involves the corpus totally and demonstrates hyperintensity with typical vertical striations. There is no spinal cord compression or loss of height in vertebral body. Axial T1-weighted MRI (**c**) shows the appearance equivalent to characteristic polka-dot sign on CT. Six months after propranolol therapy, T1W (**d**), T2W (**e**), and axial T1W (**f**) images showed no demonstrable change in the characteristics and dimensions of the lesion

Surgery (i.e., laminectomy, vertebrectomy, decompression, and ligation of segmental arteries) is recommended only when there is a progressive neurological deficit, due to the possible risk of bleeding and consumptive coagulopathy [18]. In order to reduce the risk of hemorrhage, transarterial embolization is used as an adjunctive therapy. Embolization as a single modality was used only in a few studies and the results were controversial [1, 30].

The efficacy of propranolol was shown in infantile hemangiomas (IH) incidentally in 2008 [20] and since then, infants with cutaneous [27], subglottic [4, 7], spinal [12], and hepatic hemangiomas [21] have successfully been treated with this nonselective beta blocker. It has early, intermediate, and late effects on IH, coinciding with its three mechanisms of action: vasoconstriction, inhibition of angiogenesis, and induction of endothelial cell apoptosis [31]. Vertebral hemangiomas are extremely rare in children and to the best of our knowledge, ours are the first cases reported of aggressive vertebral hemangiomas managed with propranolol. The mechanisms proposed on how propranolol induces regression of IH, may also operate in its effect on pain relief. Vasoconstriction of the vessels supplying hemangioma might relieve the pressure exerted on nerves and direct the blood pooled in tumor back to the spinal cord. Reduced expression of proangiogenic growth factors like vascular endothelial growth factor (VEGF) and increased rate of apoptosis may further act on reducing the mass of tumor causing nerve tension.

There have been less than 10 pediatric VH cases reported in the literature [2, 5, 6, 9, 15, 19, 24, 32] up to now and all of them were managed with surgery. However, most of the hemangiomas have stable clinical behavior with only a small fraction causing severe neurologic symptoms [25]. Considering the young age of patients and benign clinical features of this tumor, surgery might be preferred in cases with neurologic deficits only. Propranolol can be used effectively to control pain in patients without neurologic involvement. Our patients responded very favorably to the propranolol treatment with complete pain relief after a period of approximately 2 months. During follow-up, the lesions did not progress and were stable at 18 and 2 months, respectively. Therefore, propranolol may interfere with the progression of hemangioma and occurrence of neurologic symptoms. However, large prospective studies are needed to

observe its effects in detail. Our institution has dealt with at least 200 hemangioma cases up to now and according to our experience, response to propranolol during the first 10 days is critical to decide its effectiveness on cutaneous hemangiomas. In these two VH cases, the intensity and frequency of pain has decreased significantly in the first 10 days and disappeared totally at 2 months. Therefore, pain should be closely monitored during the first weeks of therapy in order to decide on its efficacy. Furthermore, test–therapeutic propranolol use may be employed in clinical practice when a need to exclude this rare neoplasm is necessary for differential.

Biopsy is not mandatory for the diagnosis of VH. Actually, it has a substantially low yield rate in patients with VH and we could not obtain a good specimen to have the histological confirmation of disease in case1. Not uncommonly, biopsy of aggressive hemangioma reveals nothing but blood and necrotic debris [10]. Good response to propranolol might have a test–therapeutic value in this critical step as well. Moreover, possible side effects related to propranolol, including hypotension, bradycardia, hypoglycemia, and decreased daytime activity can be monitored easily. These potential side effects may be considered more favorable than the risks of other treatment modalities.

Conclusion

We present the efficacy of propranolol in eliminating pain associated with vertebral hemangioma and contribute to the literature with two new pediatric VH cases. Rarity of this tumor limits our knowledge on behavior and course of the disease in children. Treatment modalities used in the management of adult VH cases are not feasible for children in most clinical settings. Propranolol is the most effective drug for management of infantile hemangioma cases and it is life-saving in children with aggressive subglottic hemangiomas. Considering the remarkable response of mucocutaneous hemangioma cases, we tried propranolol in our two patients who were suffering from intense pain. They responded dramatically and showed complete symptomatic relief. Therefore, propranolol may be considered as one of the non-invasive therapy options for VH-related pain in children.

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