Novel treatment (new drug/intervention; established drug/procedure in new situation)

Successful management of multi-focal hepatic infantile hemangioendothelioma using TACE/surgery followed by maintenance metronomic therapy

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Summary

Infantile hepatic hemangioendothelioma (IHE) is a rare angiogenic tumour with diverse clinical presentations and varied course ranging from spontaneous regression to life-threatening complications. The authors report a 2-year boy who presented with respiratory distress and was identified as a case of inoperable multi-focal hepatic IHE. He showed a transient response to trans-arterial-chemo-embolisation and liver resection but had progressive disease despite chemotherapy (prednisolone/vincristine/ifosfamide/cisplatin). Thereafter, he was successfully managed with metronomic therapy using cyclophosphamide and tamoxifen.

BACKGROUND

Infantile hepatic hemangioendothelioma (IHE) is a rare vascular tumour with a wide clinical spectrum ranging from spontaneous regression without any treatment to life-threatening complications.¹ No standard medical therapeutic strategies are still available for IHE. Majority of the pharmacological treatment in IHE is limited to steroids and interferon- α (IFN),² while interventional modalities include hepatic artery ligation/embolisation, hepatic resection and orthotopic liver transplantation.³ We report an, acutely symptomatic, 2-year-old boy with multi-focal hepatic IHE who was successfully managed with chemoembolisation and liver resection followed by long-term metronomic therapy with cyclophosphamide and tamoxifen.

CASE PRESENTATION

A 2-year-boy presented with massive abdominal distension of 2 months duration and respiratory distress. Systemic examination revealed a massive hepatomegaly with no ascites or other masses in abdomen. The child belonging to Indian subcontinent was the second child of a non-consanguineous marriage and his elder sibling was asymptomatic. He was delivered at term and was asymptomatic until 2 years of age.

INVESTIGATIONS

Ultrasonography (USG) of abdomen revealed hepatomegaly (≈ 20 cm) with both lobes of liver showing heterogeneous hypoechoic mass lesions. A CT scan of abdomen confirmed the USG findings and demonstrated a large lesion in the right lobe (17.8 $\times$ 14 $\times$ 13.8 cm) and one smaller focal lesion in left lobe. Serum α fetoprotein level was

within the normal range. An USG guided biopsy was performed from hepatic lesion. Based on radiologic and histopathologic analysis, the child was diagnosed as a case of inoperable multi-focal hepatic IHE.

TREATMENT

The child was started on prednisolone and vincristine, but there was no response, and his condition continued to deteriorate. Hence, to rapidly decrease the tumour size and associated respiratory distress he underwent urgent trans-arterial-chemo-embolisation (TACE) of right hepatic artery with cisplatin and doxorubicin, which was followed by three cycles of chemotherapy using ifosfamide (1.8 g/m²/day, 5 days) and cisplatin (20 mg/m²/day, 5 days). A repeat celiac and mesenteric angiogram indicated complete occlusion of right hepatic vessels, but branches of left gastric, left hepatic and superior mesenteric artery were seen indirectly supplying the tumour mass through a leash of small tortuous collateral vessels, for which no intervention could be performed due to their small calibre. Following chemoembolisation and chemotherapy, the hepatic mass reduced in size and vascularity on sonography. Hence, the patient underwent right lobectomy of liver with negative margins. Nonetheless, residual tumour deposits were noticed in the left lobe of liver, in view of which the patient received three more cycles of same chemotherapy after surgery. After six cycles of chemotherapy, a repeat CT scan revealed the presence of three small new lesions in left lobe of liver. During the course of chemotherapy, the child developed anaemia, bleeding diathesis, febrile neutropenia and constipation as side effects of the chemotherapeutic drugs.

In view of progressive lesions and ineligibility for liver transplantation due to poor general condition, the patient was started on metronomic therapy with cyclophosphamide (per oral, 50 mg/m²/day, 3 weeks a month for 1 year), and tamoxifen (per oral, 40 mg/m²/day, daily for 1 year).

OUTCOME AND FOLLOW-UP

A repeat USG after 6 months showed complete clearance of hepatic focal lesions. There were no adverse events of the metronomic therapy during the entire duration of treatment. The child now is off treatment for past 4 years, is well and has no evidence of disease recurrence.

DISCUSSION

Primary liver tumours represent 1–5% of all childhood neoplasms. Among hepatic neoplasms, the malignant tumours are more frequent than their benign counterparts.⁴ IHE, comprising 1–2% of all paediatric hepatic tumours, is a rare benign angiogenic tumour of mesenchymal origin.¹ The entity is most common in first year of life, with 85% diagnosed before 2 months of age, and is twice as common in girls as in boys.³

As per a recent classification, the hepatic hemangiomas are divided into three subtypes: focal, multi-focal and diffuse.⁵ The focal lesions include solitary and well-defined tumours, which are predominantly asymptomatic, and belong to the category of RICH-type hemangiomas (rapidly involuting congenital hemangiomas). The multi-focal lesions, characterised by multiple spherical foci in the liver, are mostly asymptomatic but some may present with high-output cardiac failure. The diffuse hepatic hemangiomas present as innumerable hepatic lesions with massive hepatomegaly causing increased intra-abdominal pressure and respiratory compromise. The clinical spectrum of disease thus ranges from completely asymptomatic condition undergoing self-regression to gradually increasing hepatic lesions manifesting with life-threatening complications. Our patient belonged to the latter category. Other reported clinical features include thrombocytopenia, consumptive coagulopathy, hypothyroidism, weight loss, jaundice and ascites. Radiographically, CT-scan is a sensitive technique for defining the extent of tumour. On ultrasonography, as in our case, lesions show a hypochoic pattern.⁶ Serum AFP levels are usually normal in patients with IHE.⁷

Cases with diffuse IHEs are rare and are associated with severe morbidity and high mortality. Though in cases of asymptomatic focal/multi-focal lesions, a wait and watch policy has been recommended⁵; in symptomatic children and in patients with diffuse lesions, the treatment should be more aggressive. The mainstay of therapy in these patients is resection of tumour. Daller *et al* reported a 62% cure rate in their study with medical or surgical treatment in all patients.¹ Moon *et al* using surgery, steroids and IFN have reported 88% survival rates.³ Zenge *et al* opined that resection be reserved for patients with life-threatening complications or suspected malignant tumours,⁸ while Samuel and Spitz recommended primary resection in all patients with symptoms with readily resectable solitary tumours.⁹ Though liver transplantation has also been recommended as a life saving option for severely patients with symptoms with multifocal IHE, new data suggest

that 5-year survival (60.6%) may not be as high as previously believed¹⁰ and whenever possible, alternative treatment options should be considered.¹¹ Steroids and IFN form the backbone of pharmacologic therapy. Steroids alone can induce complete tumour regression in 30% and in 70% of patients with IFN addition.¹² The response to steroid therapy is usually seen in 1 to 2 weeks while response to IFN is much slower. Vincristine also has been used in isolated case reports with good results.¹³ Due to the rather slow and incomplete responses, these modalities could not show benefit in our case, who presented with rapidly progressing life-threatening respiratory distress. There were three interesting aspects in our case. First, the child presented with massive hepatomegaly and respiratory distress. Due to this, he underwent emergency chemo-embolisation, which decreased the size of liver and permitted subsequent surgery. However, it is important to note that though there was regression of tumour, there was rapid development of collaterals. This emphasises that chemo-embolisation should not be used alone but only as an adjunct to other modalities. This is in concordance with earlier reports where chemoembolisation has been shown to reduce immediate morbidity but not long-term outcome.^{3 14} Second, because of availability of limited published data on use of ifosfamide and cisplatin in patients with hepatic epithelioid hemangioendothelioma, this child received six cycles of chemotherapy with ifosfamide and cisplatin with transient response. But the appearance of new lesions in liver immediately postchemotherapy asserts that this tumour is poorly responsive to conventional chemotherapy.

Third, in view of progression of the disease after standard therapy and ineligibility for liver transplantation, the child was started on antiangiogenic metronomic therapy in view of vascular origin and angiogenic nature of IHE. There was excellent response to this therapy with complete and long-term remission. This therapy inhibits new blood vessel formation, which is essential for growth and metastasis of tumour. Metronomic cyclophosphamide treatment is associated with antiangiogenic activity primarily by inducing hypoxia.¹⁵ Recent reports suggest that alkylators may also act by reducing circulating endothelial progenitor cells which actively supply cells that may participate in tumour angiogenesis.¹⁶ The role of tamoxifen as an antiangiogenic agent has been emphasised in human studies involving breast cancer and also in animal studies perusing tissues other than the breast. Angiogenesis is regulated by a balance between pro- and antiangiogenic factors. Vascular endothelial growth factor (VEGF), acting via the receptors VEGFR-1 and VEGFR-2, is a key mediator of tumour angiogenesis. The soluble form of the VEGFR-1 (sVEGFR-1) is an important negative regulator of VEGF-mediated angiogenesis. Tamoxifen has been shown to increase the ratio of sVEGFR-1 to VEGF in endothelial cells through which it exerts antiangiogenic action.¹⁷ In addition, tamoxifen has been shown to exert antiangiogenic effect by increasing matrix metalloproteinase-9 activity and generation of endostatin leading to decreased extracellular transforming growth factor- β 1 levels¹⁸ as well as VEGF.¹⁹ This antiangiogenic effect is not oestrogen mediated,^{20 21} and is dose-dependent.²² Also, tamoxifen functions as a biologic response modifier by modulating

activity of natural killer cells,²³ inhibiting effects of protein kinase C or other secondary messengers,^{24 25} and by inducing apoptosis.^{26 27} However, so far there are no data on use of tamoxifen in IHE and this is the first report on successful use of metronomic therapy with tamoxifen and cyclophosphamide in a case of IHE. The approach with metronomic therapy following surgery, conventional chemotherapy and chemoablation was extremely effective in our patient. However, given the rare occurrence of IHE and the wide biologic spectrum of disease, more reports validating the efficacy of this therapeutic strategy would be required before it can be routinely used in the management of IHE.

To conclude IHE is a low to intermediate grade vascular malignancy. The success of metronomic therapy in this angiogenic tumour confirms that therapeutic strategies involving antiangiogenic drugs along with surgery and pharmacotherapy hold promise in management of children with IHE.

Learning points

- Mainstay of treatment for symptomatic infantile hepatic hemangioendothelioma includes tumour resection, chemo-embolisation, steroids/interferon and liver transplantation in progressive/unresponsive cases.
- Antiangiogenic therapy targeting VEGF given as metronomic schedule can also yield favourable result.

Competing interests None.

Patient consent Obtained.

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