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ORIGINAL ARTICLE

Differential diagnostic features between congenital haemangioma, KHE, and congenital fibrosarcoma: a single-centre experience

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Abstract

Congenital haemangioma (CH) is a rare benign vascular tumour presenting at birth with excellent prognosis. Usually, CH regresses without treatment within the first few months of life. Kaposiform Haemangioendothelioma (KHE) is another type of vascular tumours that has been described as benign with locally aggressive potential. Although the diagnosis of vascular tumours is usually straightforward based on typical clinical presentation, yet some confusing similarities may exist with congenital sarcomas.

Conclusion: Data of cases managed at the vascular anomaly clinic during the period 2015 through 2019 were retrospectively analysed. The study included three groups of patients: cases diagnosed as congenital haemangioma (9 cases), cases of Kaposiform Haemangioendothelioma who presented in the neonatal period (7 cases), as well as cases of congenital fibrosarcoma (4 cases) that were referred to the vascular anomaly clinic because of apparent similarity with vascular tumours. The hallmark of the study was to compare clinical and imaging features in the three groups to facilitate differentiation and remove diagnostic confusion when managing these rare cases in the future.

What is Known:
- *Congenital haemangioma is a rare benign vascular tumour presenting at birth.*
- *Kaposiform Haemangioendothelioma is another type of vascular tumours that has been described as benign with locally aggressive potential.*

What is New:
- *Confusing similarities may exist between vascular tumours and congenital sarcomas.*

Keywords Fibrosarcoma · Vascular tumours · Hemangioma · Kaposiform haemangioendothelioma

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Abbreviations

CH	Congenital haemangioma
RICH	Rapidly Involuting Congenital Haemangioma
NICH	Non Involuting Congenital Haemangioma
PICH	Partially Involuting Congenital Haemangioma
KHE	Kaposiform Haemangioendothelioma
PACS	Picture Archiving and Communication system

Introduction

Congenital haemangioma (CH) is a rare benign vascular tumour presenting at birth. In contrast to infantile haemangiomas, CH typically does not grow after birth [1]. The majority of CH rapidly involute within few months to one year after birth when they are called Rapidly Involuting Congenital Haemangioma (RICH); otherwise, CH may go into partial or no involution (PICH/NICH) [1, 2].

Kaposiform Haemangioendothelioma (KHE) is another type of vascular tumours that usually present in the neonatal period or later in life [3]. KHE has been described as benign with locally aggressive potential. Severe thrombocytopenia (Kasabach-Merritt phenomenon) is a unique feature of KHE that adds risk for major complications especially among those presenting in the neonatal period and young infancy [3, 4].

Although the diagnosis of vascular tumours is usually straightforward based on typical clinical presentation, yet some confusing similarities may exist with congenital sarcomas. In this report, we aim to highlight the characteristic and differentiating features of neonatal vascular tumours based on studying cases managed at our vascular anomaly clinic over the last five years.

Patients and methods

Data of cases managed at the vascular anomaly clinic during the period 2015 through 2019 were retrospectively analysed. The study included three groups of patients: cases diagnosed as congenital haemangioma (CH), cases of Kaposiform Haemangioendothelioma (KHE) who presented in the neonatal period, as well as cases of congenital fibrosarcoma that were referred to the vascular anomaly clinic because of apparent similarity with vascular tumours. We excluded cases of infantile haemangioma (most common vascular tumour) as well as

Table 1 Summary of the differentiating features between Congenital haemangioma (CH), Kaposiform Haemangioendothelioma (KHE), and Congenital fibrosarcoma

	Congenital haemangioma (CH)	Kaposiform Haemangioendothelioma (KHE)	Congenital fibrosarcoma
Common site	Head and neck (nape), limbs	Lower limbs, face	Lower limbs
Course	Growth is complete at birth with involution over months (RICH), or stationary course (NICH)	Rapidly and diffusely growing with ***trans-spatial spread*** and compression	Rapidly growing infiltrative mass
Clinical features	Localized round or oval, exophytic, cutaneous and/or subcutaneous swelling. Red to blue colour, sometimes with ***central pallor or surrounding peripheral halo.*** Size is variable usually more than five centimetres. Lesions show characteristic ***compressibility.***	***Diffuse*** soft tissue lesion with erythematous papules, plaques, or nodules. ***Indurated purple tumours*** associated with lymphoedema.	Red or bluish in colour often with surface telangiectasia due to stretching of skin over the fast-growing tense tumor. Variable size. ***Solid (firm)*** in consistency.
Systemic manifestations	Unless very large, CH are not associated with systemic manifestations (heart failure). Mild consumption of coagulation factors not associated with bleeding issues and tends to ***self-resolve in 1 to 2 weeks.***	***Kasabach Merritt Phenomenon***: ***severe thrombocytopenia*** and coagulopathy, cutaneous purpura, and severe anaemia.	Massive bleeding may be associated with moderate thrombocytopenia, mild hypofibrinogenemia and increased fibrin degradation products.
Investigations	Investigations only needed for atypical appearance. Ultrasound: soft tissue mass with high-flow pattern (arterial). MRI: soft tissue mass (hyperintense signal on T2WI, hypointense signal on T1WI) with characteristic multiple signal voids (representing high flow vessels), and post-contrast enhancement.	***Thrombocytopenia*** is a characteristic finding. MRI: soft tissue lesion with diffuse post-contrast enhancement and ***ill-defined margins*** exhibiting hyperintense signal on T2WI and decreased signal on T1WI. ***Subcutaneous thickening*** and ***trans-spatial spread*** through deeper adjacent structures.	***Biopsy is mandatory***. Imaging: intra-lesional haemorrhage with evidence of infiltration of underlying muscle and bone
Treatment	Expectant treatment. Excision for non-involuting types.	Oral prednisolone + Vincristine Sirolimus	Excision ± Chemotherapy

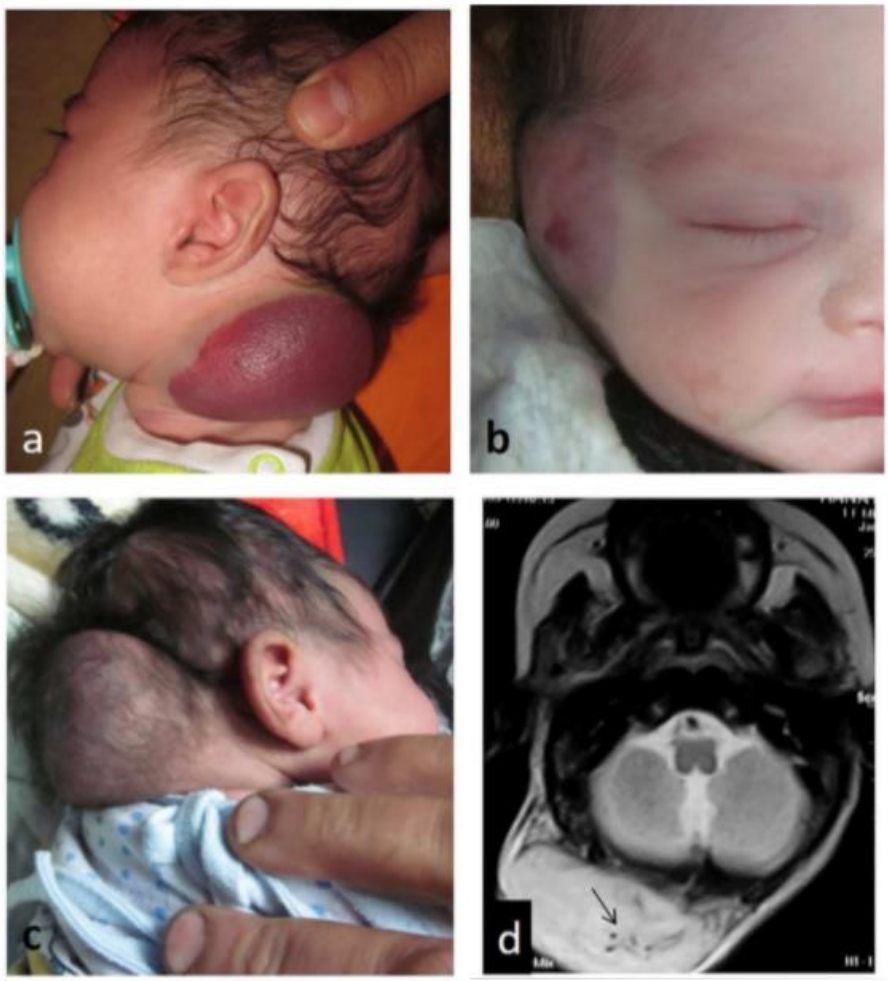

Fig. 1 Congenital haemangioma in the head and neck (three different cases). Note the typical red colour of the lesions in (**a**) and (**b**), while the overlying skin in (**c**) was almost normal. (**d**) MRI of the occipital lesion (the same case in c) to confirm the diagnosis of congenital haemangioma demonstrating soft tissue mass with hyperintense signal in T2WI and intra-lesional flow voids (arrow)

visceral haemangiomas that would be discussed in separate reports. The study was approved through expedited review by the scientific committee of the department of paediatric surgery.

Available data included clinical presentation, digital photographs of the lesions, investigations, treatment, and followup. Imaging studies of included cases were retrieved for re-examination from the hospital Picture Archiving and Communication system (PACS). The hallmark of the study was to compare clinical and imaging features in the three groups to facilitate differentiation and remove diagnostic confusion when managing these rare cases in the future.

Results

The study included nine cases of CH, seven cases of neonatal KHE, and four cases of congenital fibrosarcoma. Table 1 summarizes the differentiating features between the three groups.

Congenital haemangioma (9 cases)

There were 5 males and 4 females. Lesions appeared as localized round or oval, exophytic, cutaneous and/or subcutaneous swellings (Fig. 1). The typical colour was red; sometimes purple/blue. Central pallor was noticed in some lesions, others were surrounded by a peripheral halo (Fig. 2a, b). Common sites were the head and neck (4 cases; Fig. 1), limbs (4 cases; Figs. 2 and 3), and one case in the back (Fig. 4). Size was variable usually more than 5 cm in diameter. Lesions showed the characteristic compressibility of vascular swellings. Investigations were ordered for atypical appearance (Fig. 1c,d) or for large lesions to identify their deep extension (Figs. 2 and 3). The imaging features were 'more or less' like infantile haemangioma. Ultrasound showed soft tissue mass with high-flow pattern (arterial). In MRI, the mass showed hyperintense signal on T2WI, hypointense signal on T1WI, with characteristic multiple signal voids (representing high flow vessels), and post-contrast enhancement. Despite having

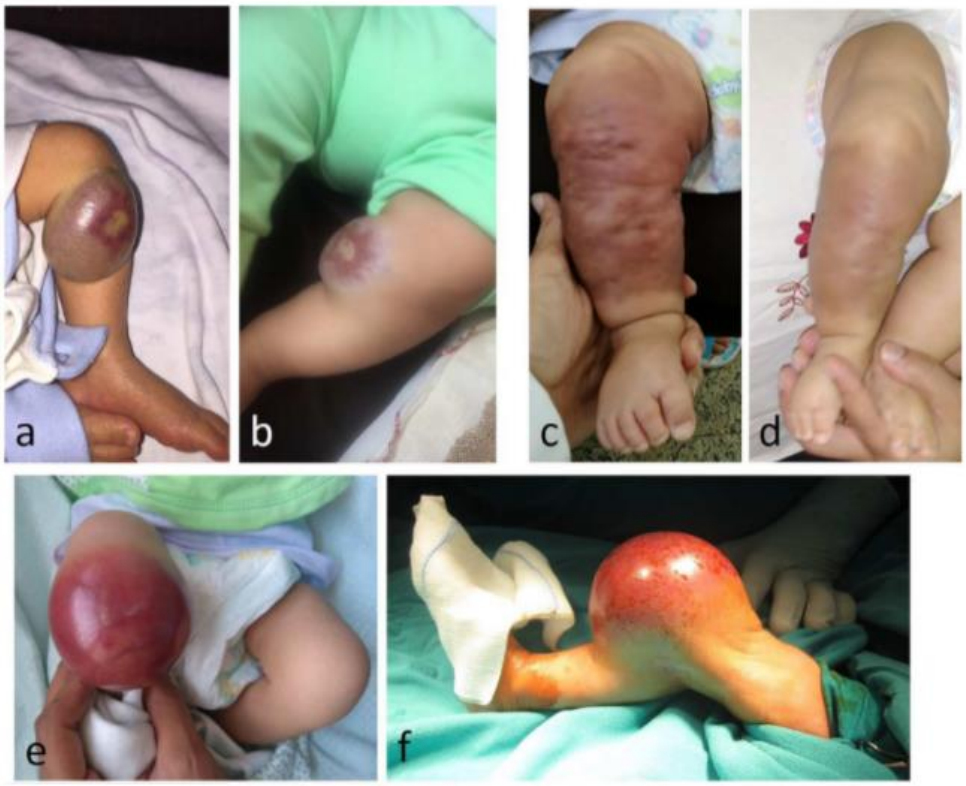

Fig. 2 Differential diagnosis of lower limb swelling in the neonatal period. (**a** and **b**) Congenital haemangioma at presentation and few weeks later (rapidly involuting congenital haemangioma); note: the presence of central and peripheral pallor. (**c** and **d**) A case of KHE of the right leg at presentation and 2 months later after start of treatment; note: the diffuse distribution and dusky colour of the lesion in c, which showed good response to treatment in d. (**e** and **f**) A case of congenital sarcoma underwent excision and postoperative chemotherapy

a doubtful role in management of CH, oral propranolol (2 mg/kg/day in three divided doses) has been initially prescribed for most cases (especially large swellings) and was shortly discontinued after start of involution. A benign course with satisfactory outcome was achieved in five cases (rapid involution within the first year of life; Fig. 2 and 3), while four cases were lost to followup.

Kaposiform Haemangioendothelioma (7 cases)

There were 5 males and 2 females. KHE presented as rapidly growing soft tissue mass with erythematous papules, plaques, or nodules. Lesions were characteristically diffuse, indurated, and dusky red in colour (Fig. 2c and 5a). The most common site was the lower limbs (3 cases; Fig. 2c), followed by the face (2 cases; Fig. 5), abdominal wall (1 case), and suprapubic (1 case; Fig. 6). MRI was superior in identifying the deeper extent of the lesion. Typical MR imaging features included soft tissue lesion with ill-defined margins exhibiting hyperintense signal on T2WI and decreased signal on T1WI. Intralesional multiple signal voids indicate for the high flow vessels with diffuse post-contrast enhancement (Fig. 6c). Subcutaneous thickening and trans-spatial spread through deeper adjacent structures (muscle and fascia) were common findings (Fig. 6b). The presence of thrombocytopenia (Kasabach Merritt Phenomenon) was a constant finding confirming the diagnosis and eliminating the need for tissue biopsy. According to consensus guidelines, oral prednisolone (2 mg/kg/day) combined with weekly vincristine infusion was the mainstay for the management of associated thrombocytopenia. Initially, vincristine was administrated in weekly doses (0.05 mg/kg) to correct thrombocytopenia, then tapered to a single dose every 2 weeks till reduction of tumour size. Satisfactory response (normalized platelet count and tumour regression) was achieved in most cases within 4–8 weeks from start of treatment (Fig. 5). Followup ranged from 1 to 5 years (mean 2.9 years; median 3 years. Mild residual skin discoloration, atrophy, and minimal oedema were noticed especially in lesions affecting lower limbs. One case had refractory thrombocytopenia for which a biopsy was taken from the

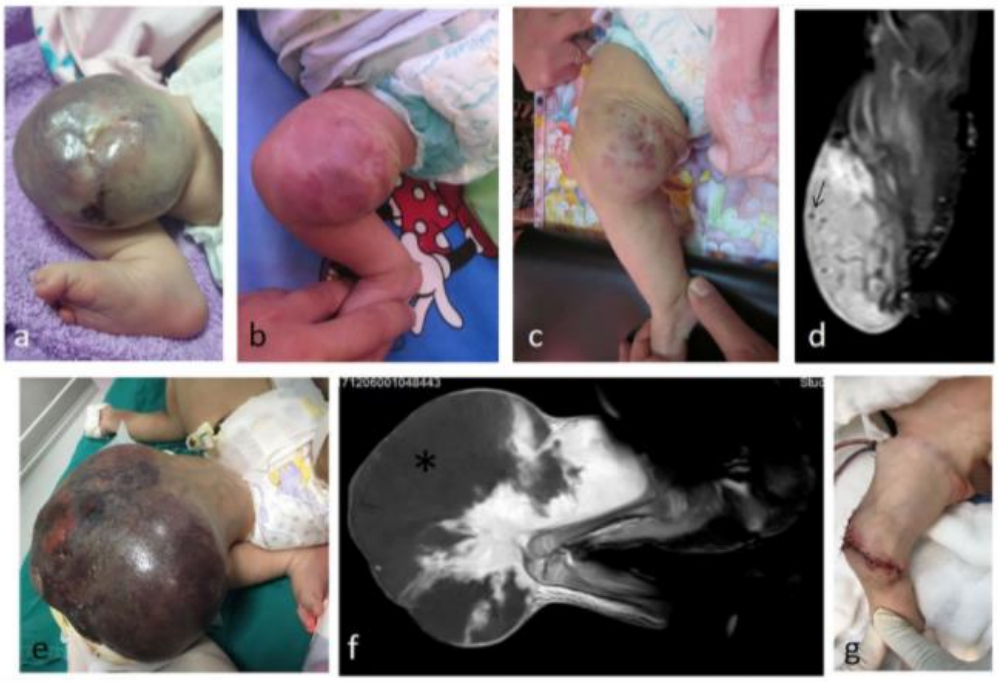

Fig. 3 Differential diagnosis between a case of congenital haemangioma (upper row: a, b, c, and d) and a case of congenital fibrosarcoma (lower row: e, f, g). Upper row (congenital haemangioma): (**a**) Female patient presenting at birth with a large mass (left thigh) showing characteristic compressibility of vascular swellings. At followup, the mass showed rapid involution by decrease in size at the age of 2 and 4 months (**b** and **c**, respectively). (**d**) Imaging was ordered at presentation (MRI T2WI, fat suppression) showing typical hyperintense soft tissue mass with intralesional flow voids (arrow). Lower row (congenital sarcoma): (**e**) Male patient presenting at birth with a large mass (left thigh); (**f**) MRI was ordered showing soft tissue mass with post contrast enhancement and areas of haemorrhage/necrosis (*); (**g**) surgical excision was performed confirming the histopathological diagnosis of fibrosarcoma

lesion to confirm the diagnosis, and a second line treatment in the form of oral Sirolimus was started (0.5 mg/m^2 every 12 h, then dose adjusted according to trough level) [5]. This case showed good response with the new line of treatment (improved platelet count) and is still under follow up (Fig. 6).

Congenital fibrosarcoma (4 cases)

There were 2 males and 2 females. The tumour was solid (firm) in consistency (in contrast to compressibility of congenital haemangioma). The most common site was the lower limbs (3 cases; Figs. 2d and 3e), and one case presented with a back swelling (Fig. 4d). The size of the lesion was variable. Imaging showed intra-lesional haemorrhage (Fig. 3f) with evidence of infiltration of underlying muscle and bone (Fig. 4e). Excisional biopsy was the rule with post-operative chemotherapy. Pathology was conclusive for infantile fibrosarcoma in the four cases. Patients were started on 'ARST3P1' protocol with vincristine, actinomycin D and cyclophosphamide (VAC); and re-evaluation was performed after 2 cycles. The indication for postoperative chemotherapy was either incomplete excision as reported by the operator (two cases) or infiltrative margins in the pathological specimen (two cases). Tumour recurrence occurred in the former two cases that required re-excision. However, the outcome was favourable in all four cases (tumour-free through follow up period that ranged from 1 to 4 years; mean 2.25 years).

Discussion

Vascular anomalies comprise a diverse spectrum of lesions involving almost all parts of the body. Using different and confusing terminology has been a great obstacle for the development in this field. In 1982, Mulliken and Glowacki proposed their famous classification, which has been adopted and modified by the International Society for the Study of Vascular Anomalies (ISSVA) in 1996 with further update in 2014 [6, 7]. The classification differentiates pathologically between vascular tumours and malformations. The former mainly includes haemangiomas, KHE, and tufted angiomas; while the latter is subclassified into low flow malformations (capillary, venous, lymphatic), high flow (arteriovenous), and combined malformations [7]. The widespread acceptance of

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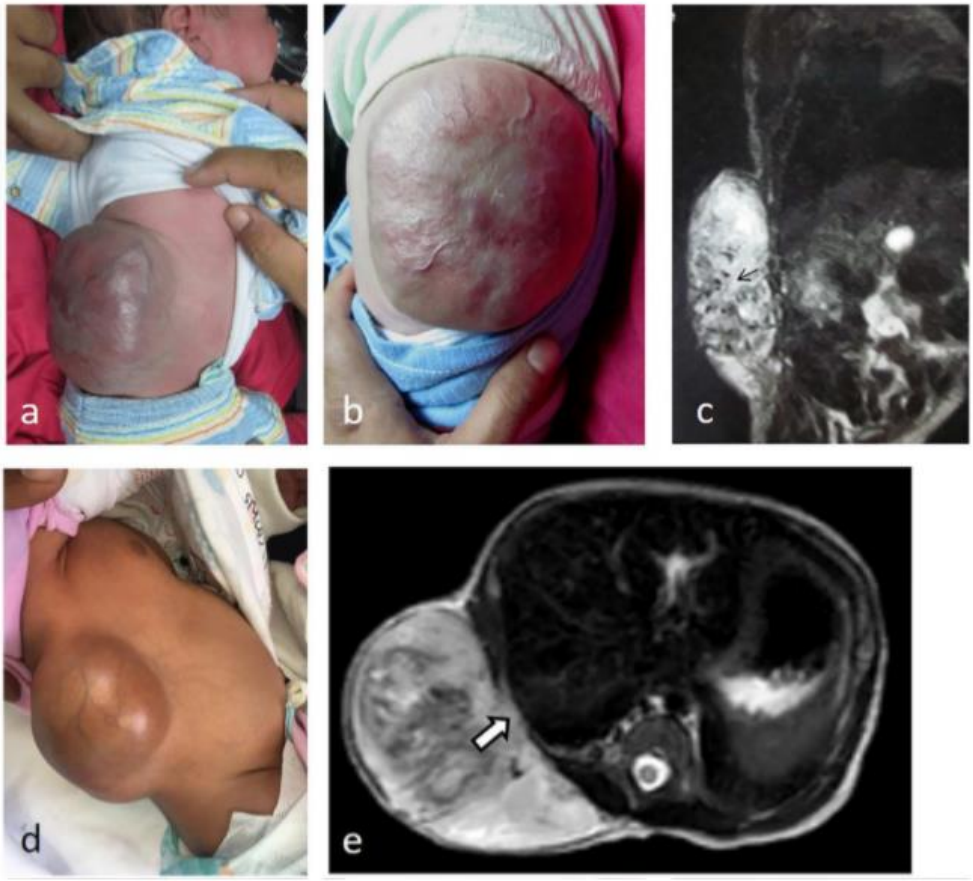

Fig. 4 Differential diagnosis of a large back swelling in the neonatal period: a case of congenital haemangioma (upper row: a, b, and c); and a case of congenital fibrosarcoma (lower row: d, and e). Upper row (congenital haemangioma): (**a** and **b**) large back swelling (about 9 x 7 cm) characteristically compressible and with central pallor. (**c**) MRI T2WI, fat suppression) showing typical hyper-intense soft tissue mass with intra-lesional flow voids (black arrow). Lower row (congenital sarcoma): (**d**) large firm back swelling. e) MRI T2WI demonstrating heterogenous soft tissue mass with infiltration of underlying chest wall muscles that appear interrupted (white thick arrow)

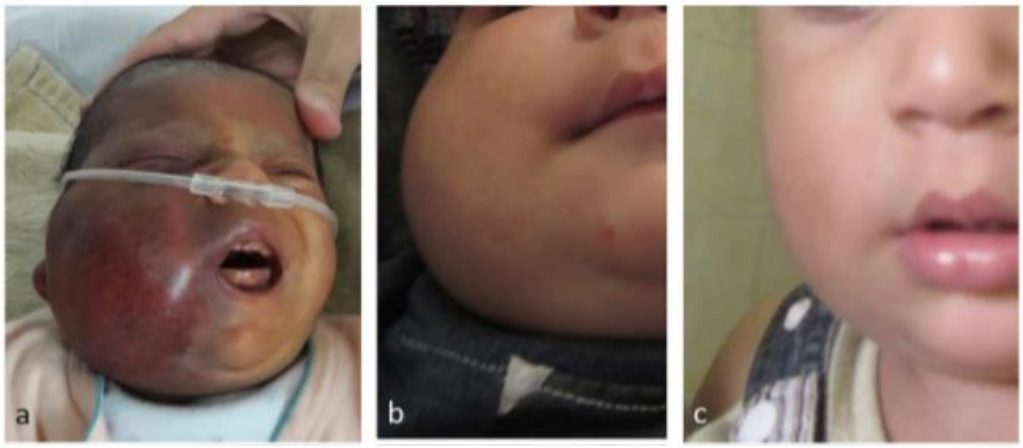

Fig. 5 A case of KHE affecting the face showing excellent response (tumor regression) with medical treatment. The digital photography of the lesion at 1 month of age, 3 months, and 17 months (**a**, **b**, and **c**, respectively)

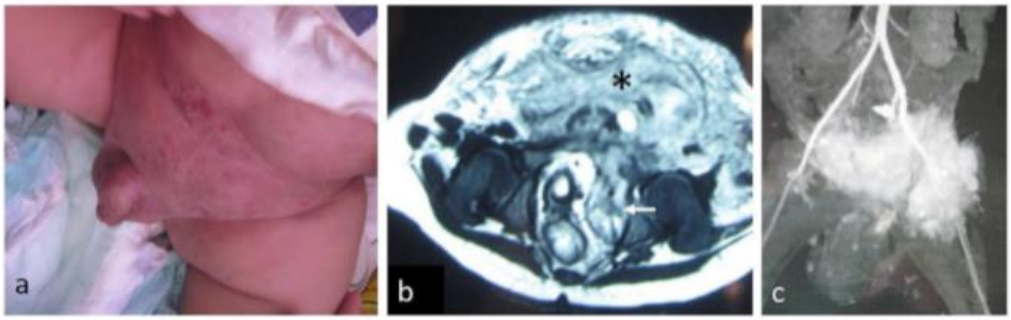

Fig. 6 A case of KHE presenting with a diffuse subcutaneous swelling in the supra-pubic region (**a**) and associated with thrombocytopenia. (**b**) MRI, T2WI of the lesion demonstrating subcutaneous thickening (*) with ill-defined margins and trans-spatial spread through deeper adjacent structures in the pelvis (arrow). (**c**) Magnetic resonance arteriography (post-contrast) demonstrating diffuse contrast enhancement of the lesion

the new pathological classification, in addition to the development of multidisciplinary teams to manage vascular anomalies has greatly improved our understanding and management of these cases [8].

Congenital haemangiomas (CH) have been recognised as a separate entity from the more common infantile haemangiomas in 1996 [2]. CH are fully grown at birth lacking the characteristic postnatal proliferative phase of infantile haemangioma [1, 2]. Another difference was the absence of female predominance which is well documented with infantile haemangiomas [1]. At the histological level, CH are GLUT-1 negative, which is considered another distinguishing feature from infantile haemangiomas [1]. Recent studies have demonstrated specific gene mutations to be associated with CH [2]. Congenital haemangiomas (CH) are rare benign lesions that usually regress without treatment within the first few months of life with excellent prognosis. CH present as a red/purple exophytic soft tissue mass often surrounded by a pale halo. Sometimes, central ulceration or scar may be present. Unless very large, CH are not associated with systemic manifestations (heart failure). Biopsy and/or surgical excision are rarely indicated except for non-involuting congenital haemangiomas and when the differential diagnosis with sarcomas cannot be ruled out. Compressibility of the lesion is usually indicative for the vascular nature of the tumour. However, for large and atypical lesions, MRI can help to differentiate CH from other neonatal masses [9]. Confusion with other high flow vascular lesions (arteriovenous malformation) is possible. The latter typically lacks the soft tissue component of the tumour when it is mostly formed of a leach of serpiginous vessels with high blood flow through abnormal arteriovenous communications [9].

Kaposiform Haemangioendothelioma is another type of vascular tumours that usually present in the neonatal period. It has been described as locally aggressive benign tumour with rapid growth and infiltration before final regression [3, 4]. Another potential morbidity may be related to the associated coagulopathy (thrombocytopenia). The later represent a life-threatening complication and is an indication for early and aggressive treatment [3]. Several drugs have been used including vincristine. More recently, sirolimus has been used successfully to induce tumour regression in cases with KHE [4]. Typically, KHE present with diffuse indurated skin lesions, dusky red in colour, with deep trans-spatial spread through underlying fascia and muscles. MRI is used to identify the deep extension of lesions and response to treatment at follow up. Although KHE may appear very aggressive at presentation (especially in lesions affecting the face), yet the responsiveness to medical treatment is generally satisfactory resulting in tumour regression with minimal residual skin changes.

Congenital fibrosarcoma (CFS) is a rare malignant mesenchymal neoplasm of the fibroblasts that can be present at birth or can develop during early childhood. It belongs to the non-rhabdomyosarcoma group. It usually manifests as a rapidly growing vascularized mass and is commonly seen in the extremities followed by the head and neck, and trunk [10–13]. The presence of red or bluish cutaneous/subcutaneous lesions encourages initial referral of these cases to the vascular anomaly clinic. These highly vascular malignant tumours resemble congenital vascular tumours in the most advanced imaging modalities when they demonstrate similar high flow vessels [14]. Reaching the proper diagnosis in such cases depends on several factors taking into consideration the clinical, radiological, and pathological aspects. As it carries a favourable prognosis, upfront surgical excision is advised if complete gross removal of the tumour can be achieved without affecting vital structures nor causing permanent disability. If excision is not possible, starting with chemotherapy may be recommended to decrease the tumour size and make its resection possible [15]. Chemotherapy protocols mostly include vincristine and actinomycin D in European studies [15]; or vincristine, actinomycin D and cyclophosphamide (VAC) in some north American protocols [16]. In this report, the included four cases of congenital fibrosarcoma had favourable outcome. Similarly, a favourable outcome was reported in a large series of 50 infants with infantile fibrosarcoma (3-year event-free survival and overall survival were 84.0 and 94%, respectively) [15].

Conclusion

Congenital haemangioma, Kaposiform Haemangioendothelioma, and congenital fibrosarcoma are highly vascular tumours that can be present in the neonatal period. Although these represent three different pathologies with different behaviour, yet they usually share a favourable prognosis. However, prompt differentiation between the three different categories is of utmost importance as each has a completely different protocol of management.

Authors' contributions AAAZ conceived of the study and participated in its design. AAAZ, SAM, NHA, MME, MA, SME and IAR participated in data acquisition. AAAZ, SAM, and IAR participated in the analysis and interpretation of data. AAAZ, MME, IAR drafted the manuscript. MA, EAA, and OE performed critical revision. All authors read and approved the final manuscript.

Data and materials availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability N/A

Declarations

Ethics approval and consent to participate Owing to the retrospective nature of the study, an IRB number was not required, and the study was approved through expedited review by the scientific/ethical committee of the surgery department (Faculty of Medicine, Ain Shams University).

Consent for publication Patient identity did not appear in any part of the manuscript; therefore, consent for publication was not required.

Conflict of interest The authors declare no competing interests.

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