

A rare presentation of Maffucci syndrome: A case report and literature review

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Abstract. Maffucci syndrome is an extremely rare disease which can manifest symptoms as early as childhood. It is estimated that there have been <300 cases reported globally; however, this number is likely to be an underestimate. Maffucci syndrome is characterized by multiple enchondromas and soft tissue hemangiomas, which can cause growth and developmental malformations. In addition to bone deformities, pathological fractures and a loss of mobility, patients with Maffucci syndrome may develop secondary central chondrosarcoma and have a higher risk of developing non-skeletal malignant tumors, such as gliomas and mesenchymal ovarian tumors. The present study provides information for clinicians about this disease through the use of imaging, physical examinations, clinical manifestations and the treatment strategy used. There is need to summarize the existing cases of this disease around the world and produce an effective framework for the diagnosis, treatment and prevention of Maffucci syndrome, in order to better understand this disease. The present study reports on a 15-year-old male diagnosed with Maffucci syndrome. Due to the risk of malignant tumor development in the absence of effective treatment, regular and careful observation through monitoring of tumor markers and imaging studies is important for patients with Maffucci syndrome. As cases of this disease are rare and case data is limited, it is difficult to create a clear treatment plan. There is an urgent need to establish a case database of

Maffucci syndrome patients and explore its pathogenesis for early diagnosis, treatment and prevention of disease.

Introduction

Maffucci syndrome, also known as chondrodysplasia with hemangioma or enchondroma with multiple cavernous hemangiomas, was first reported by Maffucci in 1881 as a rare disorder (1). There are <300 cases of Maffucci syndrome reported globally to date, however, the number of case reports is likely an underestimate due to the economic and scientific research expertise of the regions where the majority of case studies have been reported (1,2). In addition, medical professionals in certain regions may lack awareness of the disease. Maffucci syndrome is characterized by vascular and bone lesions, with patients reporting multiple enchondromas and vascular malformations, mostly affecting the skin, particularly on the upper and lower extremities (3). Previous studies have shown that non-hereditary mutations in isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase 2 (IDH2) genes are closely related to the pathogenesis of Maffucci syndrome (4,5). These mutations serve an important role in the occurrence of numerous types of malignant tumors, including intrahepatic cholangiocarcinoma, acute myeloid leukemia, glioma and oral squamous cell carcinoma (5).

Maffucci syndrome is extremely rare and there is limited knowledge about this disease. There are a few hundred cases in the world and there is no definitive agreement on the pathogenesis and main treatment methods for this disease (1,2). The present case study provides information for clinicians about Maffucci syndrome by reporting imaging results, physical examinations, clinical manifestations and the strategy used to treat the patient. The present study aimed to establish a worldwide case database and present a summarize of existing research regarding the characteristics, etiology, provisional diagnosis, differential diagnosis, treatment and prevention of Maffucci syndrome, to improve understanding of this disease.

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Case report

A 15-year-old male presented to Changzhi Yunfeng hospital in August 2018 (Changzhi, China) with a 9 year history of

multiple nodules on both upper limbs and left hand nodule bleeding for 1 day. There was no obvious cause for the initial occurrence of multiple nodules in the bilateral upper limbs, particularly in the left limb, which presented without itching and pain. Having visited a number of hospitals, the patient had not received a clear diagnosis. The patient was treated in Changzhi Traditional Chinese medicine hospital (Changzhi, China) with oral Traditional Chinese Medicine (dosage unknown). The patient was admitted to Changzhi Yunfeng hospital due to bleeding of the left palm and finger nodules. Upon further diagnostic tests, the patient was diagnosed with Maffucci syndrome.

The patient was born to healthy, non-consanguineous parents and was a first-time full-term delivery, with no deformities at birth. The patient works in customer service, denied smoking and drinking and had no family medical history of Maffucci syndrome. Physical examination of the patient on admission indicated short stature, valgus deformity of the left knee joint, varus deformity of the right knee joint and 15 cm shortening of the left lower limb compared with the right lower limb. The patient had numerous light blue subcutaneous nodules of different sizes with a soft, clear boundary and no pain in his left hand. On the left upper arm, a dark red nodular lesions (~4x3 cm) and an elbow nodular lesions (~1x1 cm) could be observed. Numerous subcutaneous nodules could also be observed in the thenar of the right palm, scrotum and perineum (Fig. 1).

Radiographs demonstrated that the lower limbs, upper limbs and shoulder blades had multiple enchondromas, in addition to developmental malformations of the left humerus, radius, femur, tibia and fibula. The patient had significant bone deformities and solitary hemangioma (Fig. 2). CT scans demonstrated that the left upper and lower limbs had multiple endophytic chondromas, developmental malformations and a venous stone that could be observed in the hemangioma of the hand (Fig. 3). Surgical resection of the diseased tissue and pathological examination were recommended. The patient refused orthopaedic surgery to remove the focus and requested conservative treatment. The patient's hemangioma involved a large amount of skin and soft tissue, but there was no pain or limb dysfunction reported. Since conservative treatment options for Maffucci syndrome are currently lacking, it was recommended for the patient to be admitted to a hospital with a higher level of expertise for further diagnosis and treatment. The patient was instructed to undergo regular medical review, closely monitor the signs of malignant transformation of endophytic chondroma and multiple hemangioma, seek early treatment and prevent pathological fractures.

According to patient follow-up, the patient had undergone resection of the focus at Shanghai traditional Chinese Medicine Hospital (Shanghai, China) and postoperative nodule bleeding was well controlled. As the patient underwent the removal of skin nodules, these images were not re-photographed. Pathological results reported cavernous hemangioma with thrombosis in the patient. However, no IDH1 or IDH2 gene mutations were detected in peripheral blood or tumor tissue DNA. The patient had two major clinical symptoms of multiple endophytic chondroma and hemangioma, therefore Maffucci syndrome was diagnosed. The patient presented with significant skeletal deformity, but

their current condition was relatively stable and the patient had no intention of orthopedic surgery. It was recommended to the patient to engage in follow-up studies to monitor the changes in their condition.

Discussion

Literature search. Certain types of malignant tumor have a risk of being associated with Maffucci syndrome, according to previously published case reports (3,4). The present study analyzed Maffucci syndrome according to case reports published in the Web of Science Core Collection database (webofscience.com/wos/woscc/basic-search; accessed July 20, 2022). The keywords used in the literature search were 'Maffucci' and 'case'.

The VOSviewer (version 1.6.17) software was used for constructing and visualizing bibliometric networks (vosviewer.com). Based on literature search results, Maffucci syndrome was reported in 248 case reports in 45 countries, with the highest number of reports conducted in Italy (n=66) and the USA (n=63). The majority of the top 10 countries that reported cases of Maffucci syndrome in the literature review were located in Europe and the USA, which may indicate that Maffucci syndrome is more likely to occur in Caucasian populations in these countries (Table I, Fig. 4). However, the publication of case reports can be related to the economic status and scientific research expertise of the region. Therefore, the absence of reports of Maffucci syndrome in certain regions does not mean there is no incidence of disease in these regions, as case studies require a large amount of data to support publication. The present study used VOSviewer to analyze the frequency of keywords used by previous case studies reporting Maffucci syndrome. The high-frequency subject terms were extracted using the Bibliographic Items Co-occurrence Matrix Builder (BICOMB), and a core subject term co-occurrence matrix was established. Through VOSviewer statistics of keywords in the field of Maffucci syndrome to form a co-word network diagram composed of core subject terms (Fig. 5). Meanwhile the article lists the first 10 high-frequency keywords (Table II).

Clinical characteristics and etiology. Maffucci syndrome is a rare mesodermal dysplastic disease characterized by multiple enchondromas and vascular malformations, particularly fusiform cell hemangiomas. Growth and developmental problems can result from vascular and bone malformations as early as childhood (1). Enchondroma is a common benign bone tumor in the distal extremities, characterized by chondrocyte involvement in the development of the long bones, limb shortening, pelvic tilt and scoliosis. Typically, enchondroma appears as solitary lesions, but Maffucci syndrome can cause the occurrence of multiple lesions. Enchondroma tends to be recurrent, which can lead to local bone destruction, pain and fractures, amongst other complications. Vascular lesions in patients with Maffucci syndrome are located in the subcutaneous tissue, usually distal to the extremities and demonstrate a lateral distribution, but can also involve mucosal tissues, such as the oral cavity (5). Additionally, these patients may develop secondary central chondrosarcomas and are more likely to develop non-skeletal malignancies in addition to bony masses,



Figure 1. Physical examination. (A) Dark red nodular lesions (~4x3 cm) was observed on (B) medial side of the left upper arm and (C) left elbow (~1x1 cm). (D) Finger deformity of the left hand showed several light blue (E) subcutaneous nodules of different sizes, which were (F) soft, well-defined and painless. (G) Patient stature was short. (H) Upper limb were thick and short. (I) Lower limbs were not equal in length and the left lower limb was shorter than the right lower limb by 15 cm.

bone deformities and pathological fractures. In addition to causing the malignant transformation of visceral chondromas and hemangiomas, Maffucci syndrome has been reported to be linked to brain and ovarian tumors, leukemia and oral squamous cell carcinoma (1,5-7).

The pathogenesis of Maffucci syndrome is currently unclear, but it is generally believed to be caused by non-hereditary mutations in IDH1 and IDH2 (1,7,8). Amary *et al* (1) and Pansuriya *et al* (8) reported that Maffucci syndrome is caused by somatic mosaic IDH1/2 mutations,

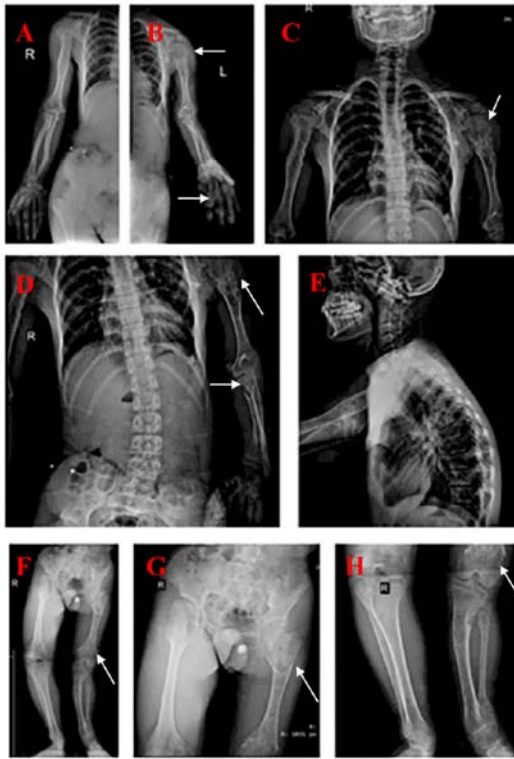


Figure 2. X-ray images of the lower limbs, upper limbs and shoulder blades demonstrate formation of multiple enchondroma. Developmental malformations of (A) R humerus, ulna and hand, (B) L hand, (C) humerus, (D) radius, (E) thoracic vertebrae, (F) L femoral condyle (G) trochanter of femur and tibia and (H) fibula. R, right; L, left; The white arrows are pointing to tumors.

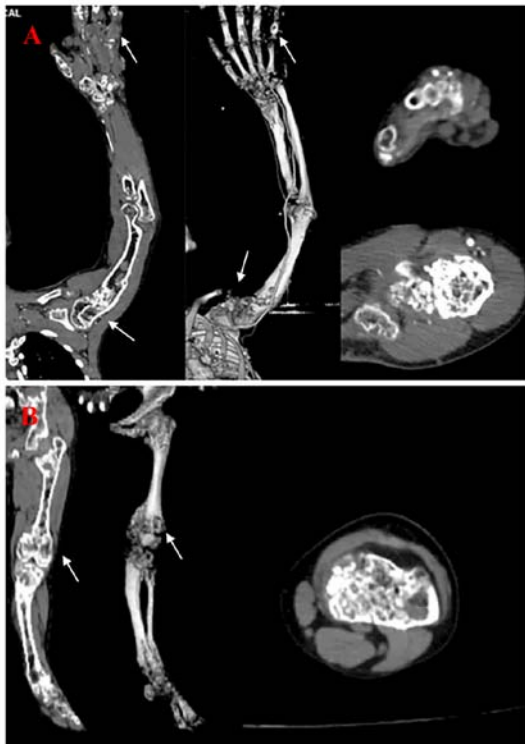


Figure 3. CT scan images of left upper limb and left lower limb. (A) Multiple endophytic chondroma, developmental malformations and a venous stone seen in the hemangioma of left upper limb and hand. (B) Left lower limb demonstrate formation of enchondroma. The white arrows are pointing to tumors.

Table I. Distribution of research on Maffucci Syndrome by country of origin

Country of origin	Case reports, n
Italy	66
USA	63
France	27
Japan	21
China	14
The Netherlands	12
England	12
Belgium	10
Germany	9
Australia	9

Table II. High-frequency keywords used in previously published case studies of Maffucci Syndrome.

Keyword	Frequency, n
Maffucci syndrome	61
Enchondromatosis	44
Chondrosarcoma	42
Ollier disease	33
Enchondroma	26
Maffucci's syndrome	24
Patient	18
Mutations	18
Glioma	14
Tumor	11

which can also be related to cases of isolated enchondroma and chondrosarcoma. >70% of reported Maffucci syndrome cases have a IDH1/2 mutation, which strongly suggests that these mutations are responsible for its pathogenesis (9). In addition, IDH1/2 mutations can cause a range of cancers, such as glioma, cholangiocarcinoma, chondrosarcoma, and acute myeloid leukemia (4). Mutations in IDH1/2 causes production of the tumor metabolite 2-hydroxyglutaric acid, which restricts cell differentiation by inhibiting the activity of chromatin-modified histones and DNA demethylation (5). Moreover, previous studies have reported mutations in the parathyroid hormone receptor 1 (PTH1R) gene in patients with multiple endophytic chondromatosis (10,11). It has been reported that a small number of patients with multiple enchondromatosis have mutations in PTH1R and these mutations lead to a decline in receptor function, which may also be a cause of Maffucci syndrome (12,13).

Diagnosis. Currently, there are no unified criteria for the diagnosis of Maffucci syndrome; however, there are a number of clinical features that can be useful for diagnosis. The development of specific diagnostic criteria need to be verified using data from a large number of case studies.

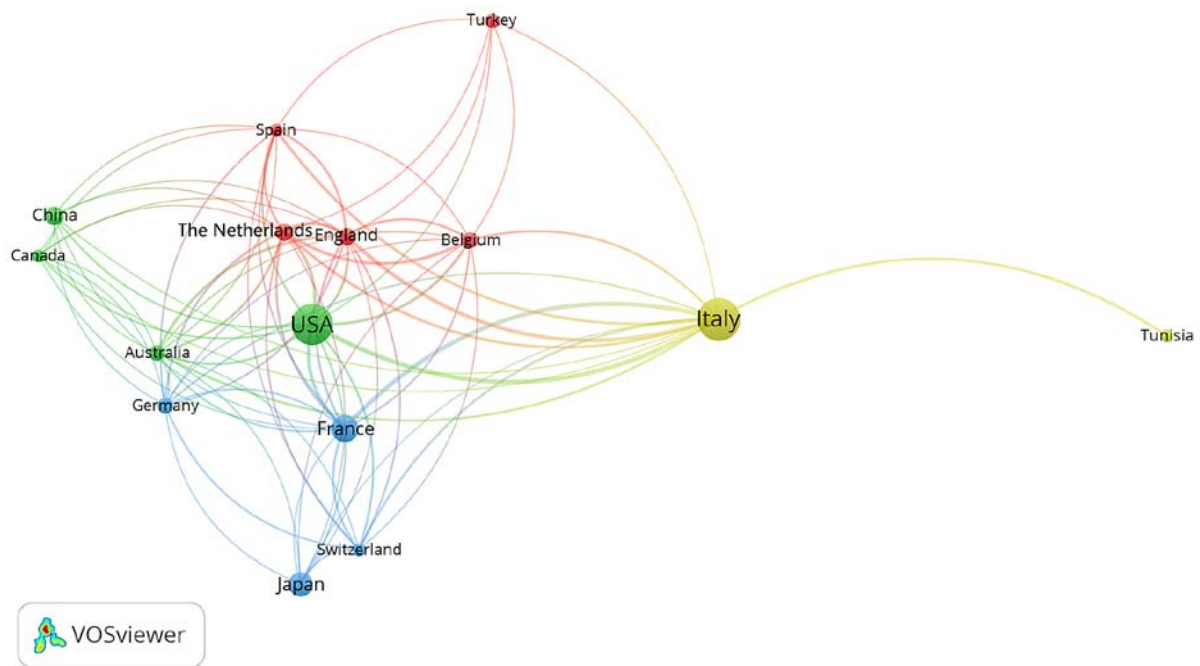


Figure 4. Cluster analysis of the distribution of research on Maffucci syndrome by country of publication.

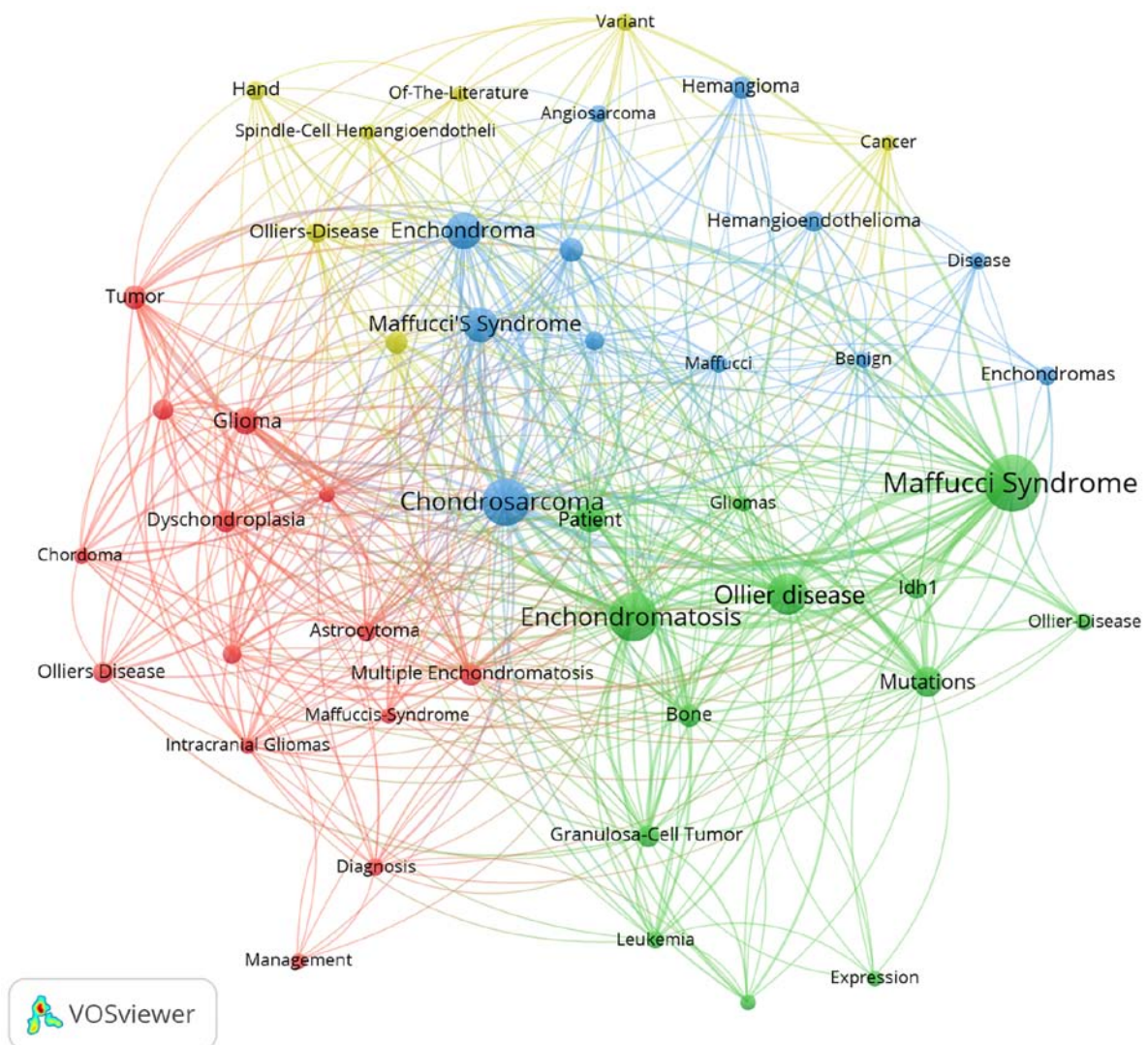


Figure 5. Cluster analysis of keywords used in previous Maffucci syndrome case studies.

The first step towards diagnosis should analyze clinical features of disease combined with patient imaging results. The clinical features were described previously in this study. When combined with imaging results, indicated that there were spots, longitudinal strips and honeycomb in the center, or side, of the bone in addition to cystic transparent areas, either presenting alone or mixed. In multiple enchondromas, it is possible to see spots of calcification in the transparent area, sometimes radial dense stripes, and often long tubular bone shortening. Small hemangiomas are difficult to observe through imaging studies, as they may only exhibit increased local soft tissue density on X-ray films, while larger multiple hemangiomas exhibit irregular thickening or nodular protrusions of soft tissue, and there are often venous stones of different sizes present, which may suggest Maffucci syndrome (14,15). In addition, it is possible to locally remove an isolated mass for pathological analysis. Pathological examinations found mainly endophytic chondroma and cavernous angioma, with or without thrombosis (3). However, performing a biopsy of diseased tissue may be unsafe and cause serious complications, such as severe bleeding, so the decision to remove diseased tissue for pathological examination should be based on the clinical situation (3,16). Molecular detection methods are used to analyze peripheral blood and tumor tissue to detect mutations in IDH1, IDH2, ELKS/RAB6-interacting/CAST family member 2 (ERC2) gene or PTH1R. For example, as an alternative diagnostic method to tissue biopsy, detection of cell-free DNA (cfDNA) can provide a highly accurate diagnostic method for Maffucci syndrome and can avoid the complications associated with tissue biopsy procedures (13). It has previously been reported that low-frequency somatic IDH1p.Arg132Cys mutations are consistently detected in hemangioma tissues and cystic blood-derived (13). Therefore, it has been suggested that genetic diagnosis of Maffucci syndrome may be improved with cfDNA sequencing, a reliable and sensitive diagnostic approach (1,8,16,17).

Differential diagnosis. A Maffucci syndrome diagnosis typically occurs for a patient during adolescence (2), as a result of the clinical manifestations of disease coupled with imaging results, as demonstrated by the patient in the present study. Combining the results from imaging studies, pathological analysis and molecular analysis, indicated that the provisional diagnosis of Maffucci syndrome was likely, however, a differential diagnosis was still required (18,19). It is important to distinguish endophytic chondroma from bone cysts, giant cell tumors of the bone, bone fibrous dysplasia and other conditions with a comparable imaging presentation. Enchondromatosis can be a symptom of either Maffucci syndrome or Ollier disease, which is also caused by IDH gene mutation (17,18). Compared with Maffucci syndrome, Ollier disease lacks the clinical manifestation of hemangioma and typically presents unilaterally. Imaging studies of patients with Ollier disease have demonstrated that there is generally no venous stone in the hemangioma and previously published studies reported that the probability of chondroma malignant transformation in Ollier disease was low (20,21). Furthermore, Maffucci syndrome needs to be distinguished from other diseases characterized by similar vascular malformations, such as blue

rubber bleb nevus syndrome, Klippel-Trenaunay syndrome and glomuvenous malformations.

Treatment and prognosis. Currently, there is no standard treatment plan for Maffucci syndrome; however, specific inhibitors of IDH1/2 have demonstrated to be beneficial for the treatment of specific malignant tumor (16). Acute myeloblastic leukemia can be effectively treated using ivosidenib or enasidenib, which inhibit IDH1 and IDH2 protein expression (22). Current research into treatments for Maffucci syndrome has been initiated by the discovery of IDH1/2 inhibitors, an important step forward for treatment of this disease, particularly for patients suffering from severe symptoms such as rapid tumor progression, dysfunction of blood system and motor system and malignant tumors (16).

At present, there is no effective treatment available for vascular lesions of Maffucci syndrome. Sirolimus, a mTOR inhibitor, can effectively treat various vascular anomalies, but further research must be performed to determine its full effectiveness (23). In general, hemangiomas should be treated to prevent patient pain, swelling and dysfunction of blood system and motor system. Currently, sclerosing agents, surgical resection, radiotherapy, embolization and chemical therapy are the most common treatments (24). Enchondromatosis could cause skeletal deformity and dysfunction, which may require orthopedic surgery, therefore malignant tumors should be resected as soon as possible (25).

To conclude, Maffucci syndrome is relatively rare, presents with diverse clinical features and has an unknown pathogenesis, therefore individual institutions are unlikely to have sufficient resources to study this disease. Therefore, there is an urgent need to summarize the existing cases around the world and produce a set of effective guidelines for the diagnosis, treatment and prevention of Maffucci syndrome, in order to gain a better understanding of this disease.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YPW, WJD, SY and ZW wrote the manuscript and analyzed patient data. YPW, SY and ZW confirm the authenticity of all the raw data. YFX, PFH and SLQ designed the study. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The patient's guardian provided written informed consent to participate in this study.

Patient consent for publication

The patient's guardian provided written informed consent for the publication of this case report and all accompanying images.

Competing interests

The authors declare that they have no competing interests.

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