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Congenital infiltrating lipomatosis of the face: A subtype of hemifacial hyperplasia

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ABSTRACT

Objective: To investigate the clinical, imaging and pathological features of congenital infiltrating lipomatosis of the face (CILF) and to discuss whether it is a subtype of hemifacial hyperplasia (HH).

Methods: Sixteen patients diagnosed with CILF were included in this study. All patients had undergone panoramic radiography and spiral CT examinations. Thirteen patients received biopsy, surgery treatment and pathological examination. The clinical documentation and imaging data were retrospectively reviewed.

Results: The cheeks (14/16), parotid glands (12/16), tongues (9/16), masticatory muscles (8/16) and the lips (7/16) were the most frequently affected soft tissue organs. The maxilla (14/16), zygoma (13/16), mandible (13/16) were involved among the maxillofacial bones. Dental malformations included macrodontia (8/16), poor formation of the roots (7/16), accelerated tooth germ development or premature eruption of permanent teeth (7/16) and missing of the permanent teeth (4/16). All malformations were restricted to one side of the face and did not trespass the middle line. Pathologically, CILF was featured by the diffuse infiltration of redundant mature adipose tissue into the tissue of the affected organ.

Conclusion: CILF is a congenital developmental facial malformation characterized by infiltration of nonencapsulated, mature adipose tissue, resulting in facial soft and hard tissue hypertrophy and dental malformations in hemifacial structures. CILF could be considered as a subtype of HH.

1. Introduction

Congenital infiltrating lipomatosis of the face (CILF) was first described by Slavin et al. [1] in 1983. It is a rare lesion with no more than 60 cases documented in English language literature [2]. It is congenital, nonhereditary and frequently discovered soon after birth. Clinically it presents with prominent congenital facial overgrowth and deformity on one side. Dental malformations, mouth opening difficulty, sleep disorders and social psychological may also be present.

Histopathologically, CILF is characterized by diffuse infiltration of the nonencapsulated, mature lipocytes into the soft and hard tissue organs of hemifacial structure. Due to its diffuse involvement of important facial structures, clinical management of CILF is a huge challenge. Complete excision is impossible in one-stage surgery [3,4]. It is best to postpone the surgical correction until the surplus growth has completely ceased.

Hemifacial hyperplasia (HH) manifested as enlargement of multiple soft or hard tissue organs on one side of the face. It is also described as congenital hyperplasia of the facial soft and hard tissue organs on one side of the face [5,6]. HH may be a part of hemihyperplasia of the whole body [6,7]. The pathology and etiology of HH is not known. In spite of the very similar clinical presentations under these two terms, there is not enough evidence to support their association. Only recently some authors have indicated that CILF might be a subtype of HH [8].

The purpose of this study is to summarize the imaging features of CILF, so as to improve the clinical management of this disease and to

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further reveal the relationship between CILF and HH.

2. Materials and methods

2.1. Patients and clinic records

Sixteen patients diagnosed with CILF in our hospital over the period from January 2011 to December 2017 were included in this study. Family and medical history, clinical presentations, imaging findings, pathological findings and treatment course were reviewed. This study had been approved by the Institutional Review Board of School and Hospital of Stomatology Peking University (PKUSSIRB-2012084).

2.2. Imaging examinations

The maxillofacial region was scanned using a 16-row spiral computed tomography scanner (GE Optima, USA). The following scanning parameters were used: 200–380 mA (automatic exposure control); 120–140 kV; pitch: 1.625; field of view: 20 cm; reconstruction thickness: 1.25 mm. The consecutive axial images were reconstructed and stored in our picture archiving and communication system. Panoramic radiography examinations were also performed at the patients' first visits.

Two experienced oral and maxillofacial radiologists with more than 10 years' experience reviewed all the imaging documentations in consensus.

2.3. MRI examination

Four patients had undergone MRI examinations. Spin-echo sequences were used for scanning of the head and facial area. T1 weighted, T2 weighted and fat-suppressed T2 images were acquired.

2.4. Pathological examinations

Histologic examinations were performed in 13 patients. The surgical specimens had been fixed routinely in 10% neutral buffered formalin (18–48 h), processed, embedded in paraffin, and serially sectioned. Hematoxylin-eosin staining was also performed.

3. Results

3.1. Clinical records

The patients included 7 males and 9 females aging from 4 to 37 years old with the mean age of 13.9. Among them 13 cases were children or adolescents, 3 cases were adults. Eight cases occurred on the right side of the face and 8 cases occurred on the left side. All 16 patients complained of progressive facial swelling, asymmetry after birth, without pain or any other conscious symptoms. Thirteen patients had received biopsy or surgical treatments. All patients had involvement of the cheek from the infraorbital rim to the angle of the mandible.

Clinical presentations included hemifacial soft tissue hyperplasia (16/16) involving the tongues (8/16), cheeks (14/16), parotid glands (10/16), lips (6/16), eyelid (6/16) and soft palate (2/16). There was no tenderness and the involved area was soft on palpation. Nevi (2/16) were noticed on the skin over the neck. Remarkable specific dental presentations included premature eruption of permanent teeth (6/16) (Figs. 1 and 2).

3.2. Imaging findings

Panoramic radiography showed that macrodontia (8/16), poor formation of the roots (7/16), accelerated tooth germ development and premature eruption of permanent teeth (7/16), missing permanent teeth (4/16) among 16 patients (Table 1, Fig. 3).

CT shows the soft tissue hypertrophy due to the adipose tissue infiltration involving the lip (7/16), cheek (14/16), tongue (9/16), temporal region (5/16), parotid gland (12/16), masticatory muscle (8/16) and soft palate (3/16). Due to the involvement of the soft palate, the upper airway was involved in 2 patients. The involved masticatory muscles presented with hypertrophied profile and reduced CT attenuation. The mean attenuation of the affected muscles was 10 Hounsfield (Hu), while the mean attenuations of normal masticatory muscle were 55 Hu. The affected parotid gland also presented with enlarged profile and reduced attenuation (−10Hu) (Fig. 4). The muscles and parotid glands showed clear demarcations with adjacent organs.

Fifteen patients showed prominent hypertrophy of the maxillofacial bones on the affected side, including the maxilla (14/16), zygoma (13/16), mandible (13/16) and sphenoid bone (2/16) (Fig. 5). Hypertrophy of the mandibular condyle on the affected side was observed in 7 cases. Osteoma-like change of the condyle was observed in 1 case.

MRI in 4 patients showed diffuse fatty infiltration with increased thickness of subcutaneous fat on the involved side of the face. Fat tissue showed high signal intensity of the lesion on T1 and T2 weighted images and low signal intensity on fat-suppressed T2 images on MRI.

3.3. Surgical resection and outcome

Eleven patients underwent surgery treatment. Two patients underwent biopsy to confirm the diagnosis. Three patients did not undergo a biopsy or surgery. Among the 11 patients who underwent surgical treatment, 4 patients had undergone the resection with the diagnosis of lipoma of the face at the mean age of 3 years old before they visited our hospital and postoperative recurrence was observed. One patient had undergone multi-stage surgical treatment involving soft and hard tissue until the age of 37 years old, who received satisfactory treatment outcome.

3.4. Histopathologic findings

Thirteen patients had the histologic examination of the excised specimens. The histologic examination showed adipose tissue diffusely infiltrated into submucosa (8/13), dermis (4/13), skeletal muscle (6/13), parotid gland (3/13), and minor salivary glands (3/13), with absence of lipoblasts or malignant characteristics (Fig. 6).

4. Discussion

Congenital infiltrative lipomatosis frequently affects the trunk and limbs and rarely occur in the face [9]. Congenital infiltrating lipomatosis of the face (CILF) was first described by Slavin et al. [1] in 1983. It is histologically characterized by nonencapsulated, mature adipose tissue that infiltrates into the soft and hard tissue organs of the face, resulting in facial deformity and symmetry. The main characteristic of CILF described by Slavin et al. [1] included: nonencapsulated lesion containing mature lipocytes; fat tissue infiltration of adjacent muscles and soft tissue organs; absence of malignant characteristics; absence of lipoblasts; presence of fibrous elements and increased number of nerve bundle and vessels; adjacent bone hypertrophy.

CILF is rare and there are no more than 60 cases documented in the English literature [2,10]. The largest number case series searched on Pubmed is the 13 cases report of Padwa and Mulliken [11] in 2001. Since then, there have been only a few single case reports [12,13]. This report is of the largest sample size in English language literature.

CILF is congenital, nonhereditary and usually discovered after birth. There is no sex or side predilection. The main complaint is facial progressive painless swelling, deformity and asymmetry [14–16]. Some of the patients might be misdiagnosed as lipoma and received radical excision at an early age, which usually receives very limited beneficence and results in more disastrous facial esthetic problems.

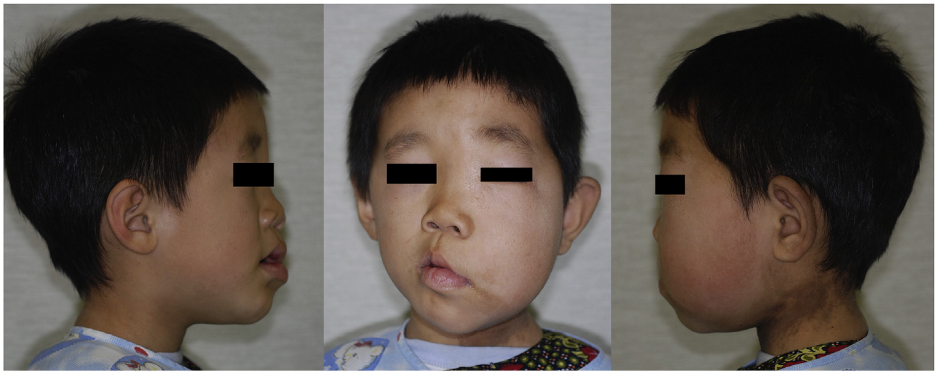

Fig. 1. Clinical photograph shows hemifacial enlargement on the left side involving the eyelid, cheek and lip. Nevi can be seen on the skin over the neck.

The etiology of CILF remains unknown. Several studies have found that postzygotic gene mutation may play a role in the pathogenesis of CILF. Capra et al. [17] reported a deletion of chromosome 1q24.3q31.1 in a girl with pituitary deficiency and CILF. Maclellan et al. [18,19] reported the presence of PIK3CA mutations in affected tissue of these individuals, implicating the possible role of PIK3 for the lipomatous change. PIK3, encoded by PIK3CA, plays a crucial role in regulating cell proliferation, adhesion, survival, and motility. The organs affected in CILF mostly derive from mesenchyme of the first and second branchial apparatus, which might locate the early gene mutation. Other factors, such as trauma, chronic irradiation, muscular metaplasia, degenerative fatty transformation, congenital cytomegalovirus infection, have been suggested as possible etiology for the lipomatous change [11,20,21].

CILF is mainly characterized by extensive and diffuse infiltration of unencapsulated, mature adipose tissue. Cheeks, parotid glands, tongues, masticatory muscles and lips are most likely to get involved. And diffuse adipose causes underlying facial skeleton hypertrophy. Maxilla, mandible and zygomatic bone are most likely to get involved. Bone changes may be associated with periosteal irritation associated with the overlying mass. Regional malformation of mesenchyme affecting bone and soft tissue or increased vascularity [22,23]. The involved bone may keep regular enlargement unless bone biopsies or surgeries had been performed. In this study, 7 of 16 cases in which condyle on the affected side was significantly hypertrophy than unaffected side, and one case had osteoma-like changes. This should be differentiated from the circumstance of “condylar hyperplasia”. CILF can also involve the temporomandibular joint leading to joint ankylosis, facial asymmetry and reduced mouth opening [15,24].

Besides soft tissue and facial bone hypertrophy, dental malformation is also an important feature of CILF. The manifestations of dental malformation include macrodontia, poor formation of the roots, accelerated tooth germ development and premature eruption of permanent teeth, missing permanent teeth [10,11,25]. Occurrence of macrodontia could possibly be related to accelerated dentoskeletal growth. Enlargement of the crowns and elongated roots could be observed. Poor formation of the root is also remarkable. Short root could be observed. Missing permanent teeth may relate to poor formation of the root. Diseases associated with accelerated tooth formation and early premature eruption are rare. Accelerated tooth germ development and early eruption could be widespread or sporadic, in either maxilla or mandible [25].

The diagnosis of CILF mainly depends on clinical presentation and imaging findings [26,27]. Panoramic radiography can provide an overall presentation of dental malformations. The CT and MRI remain the most helpful tools for radiographic diagnosis. CT can help demonstrate the lipomatous nature of mass, osseous changes and their anatomic location and relationship to surrounding structures. Diffuse fat tissue infiltration (-60HU to -120HU) and hyperplasia of multiple bones of the maxillofacial bones can be seen with three-dimensional CT. The fatty infiltration can be inhomogeneous, which may be related to intervening fibrous elements [24]. MRI is also very specific for identification of fat tissue of the organs. High signal intensity of the lesion on T1 and T2 weighted images and low signal intensity on fat-suppressed T2 images can be seen on MRI. MRI is not always reliable to differentiate CILF from well-differentiated liposarcomas.

And multiple pathological sections are needed for differential diagnosis [28]. The lesion was histologically characterized by sheet or lobules of mature normal adipocytes infiltrating trabecular bone, muscle fibers and salivary glands, absence of malignant characteristics and lipoblasts [27,29].

The differential diagnoses of CILF include vascular malformation, hemangioma, lipoma, liposarcoma, lipoblastomatosis and other overgrowth syndromes. Vascular malformation or hemangioma could be easily differentiated on CT and MRI. Most lipomas are clearly defined and well-encapsulated. Intermuscluar lipoma is ill-defined but usually restricted to one or more muscles. Well-differentiated liposarcoma and lipoblastomatosis that involve fat tissue infiltration also need to be ruled out. Liposarcoma is associated with the presence of lipoblastic

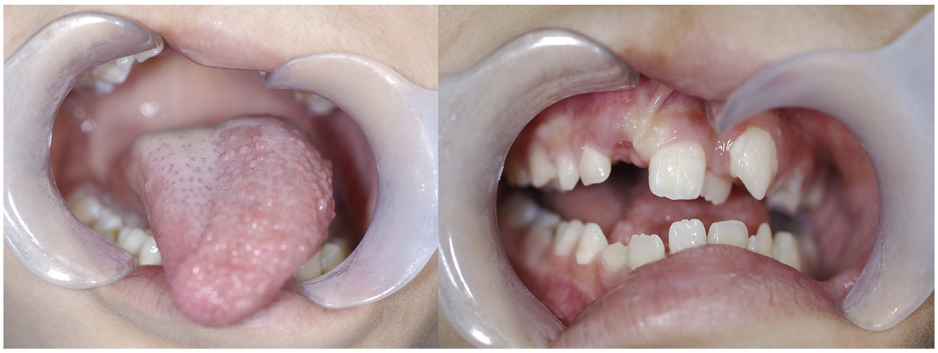

Fig. 2. Intraoral view shows hyperplasia of the left hemitongue and early eruption of 21–23.

Table 1
Clinical and Imaging Features of Congenital Infiltrating Lipomatosis of the face.

Case	Sex	Age	Side	Hypertrophy of soft tissues	Hypertrophy of bones	Condyle involved	Macrodontia	Poor formation of the roots	Accelerated tooth germ development and early eruption	Missing permanent teeth
1	F	16	L	Lip, Cheek, Tongue, Temporal region, Parotid gland	Max, Man, Zyg	N		25、34、35		22-24、26、27、36、37
2	F	23	L	Lip, Cheek, Temporal region, Parotid gland	Max, Man, Zyg	Y		24-27、34-37		
3	F	12	L	Cheek, Tongue, Soft palate, Parotid gland	Max, Man, Zyg	Y	37	25、35、36	24、27	
4	F	17	R	Masseter, Medial pterygoid, Lateral pterygoid	Max, Man, Zyg	Y	46、47			16
5	M	14	R	Cheek, Tongue, Soft palate, Parotid gland, Masseter	Max, Man, Zyg	Y		13-17、32-37		
6	F	9	R	Cheek, Tongue, Temporal region	Max, Zyg	N	16、17、46		13-17、43-47	
7	F	19	L	Cheek, Masseter	N	N				26
8	M	14	R	Lip, Cheek, Tongue, Parotid gland	Man, Zyg	N				
9	F	37	L	Soft palate, Parotid gland, Masseter, Medial pterygoid, Temporalis	Max, Zyg	Osteoma	36			
10	M	4	R	Cheek, Temporal region, Parotid gland, Masseter, Temporalis, Medial pterygoid	Max, Man, Sph	Y			16、17、46、47	
11	M	11	L	Lip, Cheek, Tongue, Temporal region, Parotid gland, Masseter Temporalis	Max, Man, Zyg, Sph	Y	26、27、36、37			
12	M	10	R	Cheek, Parotid gland, Masseter	Max, Man	N	17	14、15、16	14、15	
13	M	15	R	Cheek, Parotid gland, Masseter	Max, Zyg	N		14、15、17		13、16
14	F	5	L	Lip, Cheek, Tongue, Temporal region, Parotid gland	Max, Man, Zyg	N	26、36		23-27、32-37	
15	F	9	R	Lip, Cheek, Tongue, Parotid gland	Max, Man, Zyg	N		13、14、16、46	14、15、17、43、44	
16	M	7	L	Lip, Cheek, Tongue	Max, Man, Zyg	N	26、36		21-27、31-37	

F = female, M = male, L = left, R = right, Max = maxilla, Man = mandible, Zyg = zygomatic bone, Sph = sphenoid bone, Y = yes, N = no.

proliferation and large number of cell mitosis and pleomorphism. Lipoblastomatosis has the presence of fetal adipose tissue, which is absent in the histopathological examination of CILF tissue. Liposarcoma and lipoblastomatosis are usually located on the trunk and extremities [30].

CILF should be differentiated from other overgrowth syndromes, such as Klippel–Trenaunay-Weber syndrome, CLOVES syndrome, Proteus syndrome and segmental overgrowth with fibroadipose hyperplasia [17,31,32]. Klippel-Trenaunay-Weber syndrome is characterized by the triad of port wine stain, varicose veins and hypertrophy of bones overlying soft tissue. It is associated with hemimegalencephaly and limb hypertrophy in some cases. CLOVES syndrome is clinically characterized by congenital lipomatous overgrowth, vascular malformations (capillary, venous, lymphatic, and/or arteriovenous), epidermal nevi and scoliosis/skeletal anomalies. Soft tissue and bony overgrowth are also present in CLOVES syndrome. Proteus syndrome is characterized by the overgrowth of tissue from all three germ layers with a wide spectrum of presentations including lipomatosis, hemihypertrophy, macrodactyly, exostoses, osseous hypertrophy and linear sebaceous nevi [33]. The major manifestation of segmental overgrowth with fibroadipose hyperplasia is segmental and progressive overgrowth of subcutaneous, muscular, and visceral fibroadipose tissue. It is also sometimes associated with skeletal overgrowth. Some clinical presentations of CILF are very similar to these syndromes. However, unlike these disorders, CILF rarely involves organs outside the head and neck. Several studies have found that PIK3 gene mutation plays a role in the pathogenesis of CILF. And overgrowth syndromes like CLOVES syndrome, Proteus syndrome and fibroadipose hyperplasia present mosaic activating mutation of PIK3-AKT signaling [18]. Hence it is possible that CILF and these syndromes share some common pathogenesis.

The distinction and association between HH and CILF are rarely discussed and documented. HH was first described by Meckel [5,6] in 1822 and first reported by Wagner [7] in 1839. HH is mainly featured by facial enlargement of hard and soft tissue organs on one side. Soft tissue anomalies involve lip, buccal mucosa, uvula and tonsils. Hard tissue anomalies involve maxilla, mandible, zygoma and teeth. And other general deformities include macrodactyly, polydactyly, syndactyly, ectrodactyly, scoliosis, tilting of the pelvis and clubfoot [7]. Macrodontia and premature loss of primary teeth may be present. Rusthon [34] found that macrodontia was characteristic for HH. Rowe [35] found that the size and shape of the crown and root size, as well as rate of development, was usually abnormal if the teeth were affected. Macmillan et al. [36] stated that the characteristics of CILF were very similar to HH and they were the same disease. Kang et al. [37] also found that HH was associated with the under-reported infiltrating lipomatosis. In our opinion, CILF actually does lead to HH and should be considered as at least one subtype, or even a large proportion, of HH. The nomenclature of HH is emphasized on the clinical outcomes, while CILF is emphasized on the etiological mechanism.

There are great many controversies and challenges in the treatment of CILF. The major problems concerned include facial asymmetry and deformity, dental malocclusion, snoring or obstructive sleep apnea syndrome and psychosocial issues. Multidisciplinary collaboration and multi-stage surgical intervention are needed for patient management [3,27]. The timing of surgical interventions is of great controversy. The recurrent rate of CILF after the first surgery at early childhood was reported to range from 27.3% to 62.5% [30]. The value of aggressive extirpation must be weighed against the potential injury to the facial nerve [38]. Slavin and Kang et al. [1,37] in their early studies encouraged early aggressive resection in childhood in order to improve facial appearance and control the overgrowth. Chen and Wingerden et al. [30,39] advocated delay of the radical surgical treatment because of the high recurrent rate and the increased risk of injury to the facial nerve. They advocated more conservative treatment during childhood. And the surgery should be delayed until the end of adolescence. However, they pointed out that postponement of surgery might result in

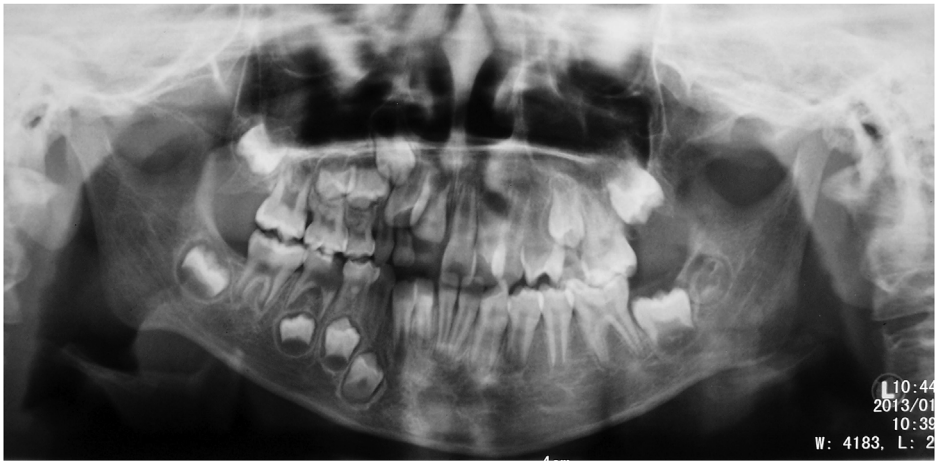

Fig. 3. Panoramic radiograph shows accelerated tooth germ development (25, 27, 37) and premature eruption of permanent teeth (21–24, 31–35) and macrodontia (26, 36) on the left side.

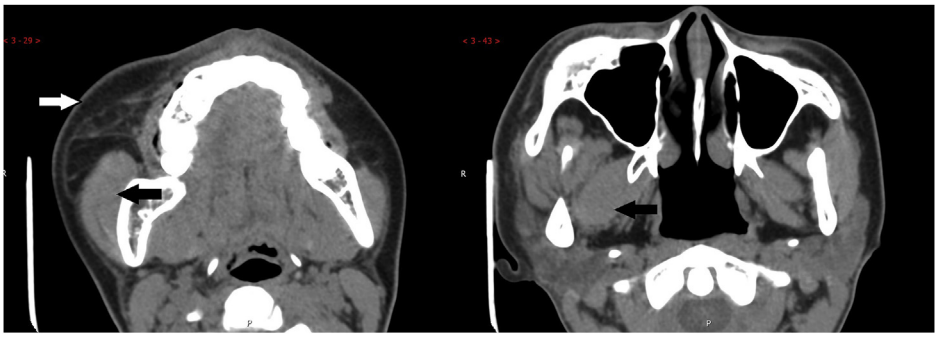

Fig. 4. Axial computed tomography shows the fat infiltration in the right cheek subcutaneous layer (white arrow) and hypertrophy of right masseter and lateral pterygoid muscle (black arrow).

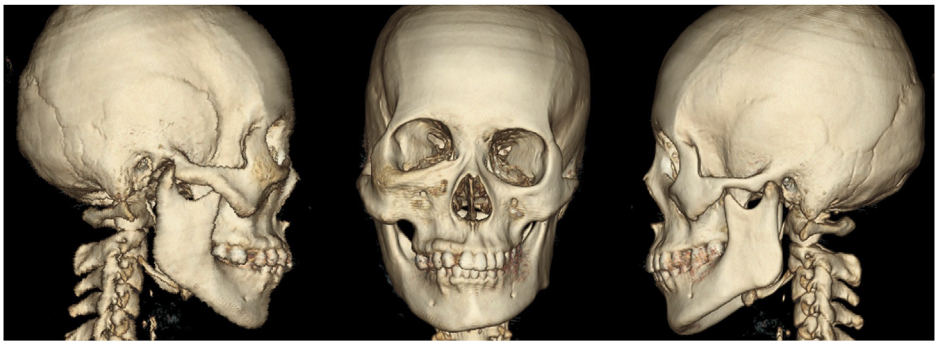

Fig. 5. Computed tomography volume rendering image shows hypertrophy of the right zygoma, maxilla, and mandible.

more extensive surgery and complex psychosocial problems. Padwa and Mulliken et al. [11] observed that growth hormone most probably has a role in recurrences. They believed that any effort to reduce the mass before the end of adolescence was bound to fail. Conservative treatment, such as liposuction, could be performed in young patients with minimal risk. This was in line with Wingerden's view. Kamal et al. [10] reported two cases of CILF in which surgery was done at the end of adolescence and no evidence of recurrence. It indicated that radical plastic surgery should be postponed until the end of adolescence.

Surgical treatment still lacks standard procedure for CILF, depending on the varying degree of deformity. Kalantary et al. [40] proposed a new multistep surgical approach toward the management of CILF. This involves initial debulking to correct the soft tissue asymmetry, followed by orthognathic surgery to correct the skeletal asymmetry, dental problems and associated malocclusion. Tracy et al. [4] reported a new therapeutic protocol involving surgical resection and targeted chemotherapy in 2013. Imatinib and celecoxib were prescribed as personalized targeted chemotherapy, which demonstrated improved facial symmetry without evidence of disease progression. Generally speaking, delay of definitive surgery has several advantages such as minimizing the chance of damage to the facial nerve, decreasing the total number of procedures, improving aesthetic problems. Conservative treatment can be performed in young patients with minimal risk. Therefore, valid diagnosis is of great importance for the treatment and management of CILF patients.

5. Conclusion

CILF is a rare disease characterized by unencapsulated, mature adipose tissue infiltrating into several facial organs on one side. CILF is

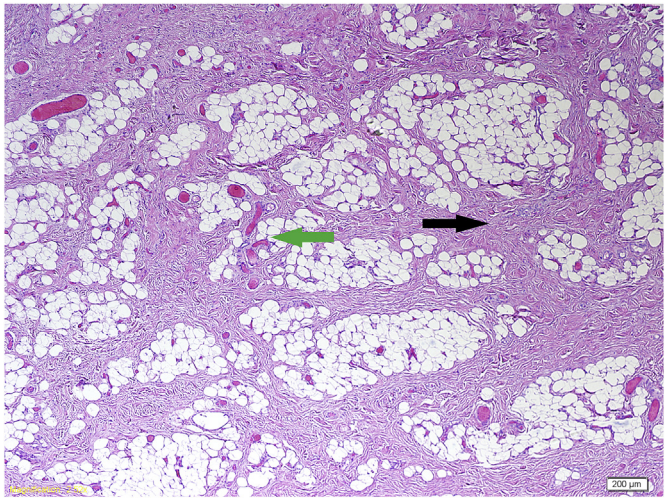

Fig. 6. Photomicrograph shows abundant mature adipocytes infiltrating fibers (black arrow), with increased number of small vessels (green arrow). Hematoxylin–eosin stain, original magnification x40. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

a kind of clinical entity lead to HH. The diagnosis could be established with clinical presentations and imaging examinations.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgement

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