International Journal of Pediatric Otorhinolaryngology 77 (2013) 2071–2074

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

Case report

Interdisciplinary management of congenital infiltrating lipomatosis

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ARTICLE INFO

Article history:
Received 23 May 2013
Received in revised form 6 August 2013
Accepted 9 August 2013
Available online 22 August 2013

Keywords:
Oncology
Benign neoplasms
Chemotherapy
Facial plastic surgery
Head and neck surgery

ABSTRACT

Congenital infiltrating lipomatosis is a benign yet locally invasive lipomatous tumor. Current treatment involves surgical excision and reconstruction of craniofacial deformity. Invasion of vital structures often makes complete resection problematic and recurrence is common. We present the case of a 15-year-old female patient with extensive congenital infiltrating lipomatosis involving the left face. A broad treatment algorithm was devised involving surgical resection as well as targeted chemotherapy. At 18 month follow-up the patient demonstrated improved facial symmetry without evidence of disease progression. Combining surgical and medical intervention may allow for a synergistic approach to controlling this rare disease.

1. Introduction

Congenital infiltrating lipomatosis (CIL) is a congenital disorder characterized by overgrowth of benign, mature adipocytes. This condition presents with unilateral facial swelling, generally involving the lower two thirds of the face. Although present at birth, more indolent cases may not present until adolescence or early adulthood. The infiltration of adipocytes is unencapsulated and does not respect tissue planes, although other malignant features are not found [1,2]. Associated soft tissue as well as bony hypertrophy are typical, and features of macrodontia and early dental eruption on the affected side are common [3]. Many patients demonstrate a cutaneous capillary blush, and mucosal neuromas are associated in some patients [1,4].

The term congenital infiltrating lipomatosis of the face was first used by Slavin et al. in 1983 in a paper that described histopathologic characteristics associated with the condition. These include infiltration of fat into surrounding tissue and bony hypertrophy; absence of malignant features; absence of lipoblasts; presence of fibrous elements; increased blood vessels, exhibiting unifocally thickened muscular walls; and increased number of nerve bundles associated with focal fibrosis [5]. CIL is extremely rare with only 36 published cases [1,2].

The management of CIL is surgical excision, however preservation of the facial nerve often necessitates a subtotal resection. The average patient with CIL undergoes at least 3 surgical procedures [6]. Timing of surgery is controversial. Current recommendations include temporizing measures such as liposuction and lip elevation procedures as warranted in childhood; with aggressive resection delayed until after completion of the growth of the bony skeleton [4,7].

2. Presentation and management

A 15-year-old female patient was seen in consultation with the Department of Otolaryngology – Pediatric Facial Plastic Surgery with regards to facial asymmetry. She reported a past diagnosis of CIL and had undergone at least 6 surgical procedures in the past. In addition she had been treated previously with thalidomide and celexocib, with some success in delaying disease progression. As a case report, this publication was granted "exempt" status by the Tufts Health Science Campus Institutional Review Board. Consent for publication and presentation of health information was obtained from both the patient and her mother; and documented per policy of the Tufts Health Science Campus Institutional Review Board.

At the time of evaluation, she reported significant increase in her facial asymmetry with significant left facial hypertrophy/swelling over the past 1–2 years. The patient reported associated

Abbreviations: CIL, congenital infiltrating lipomatosis; CT, computed tomography; MR, magnetic resonance; PDGF-R, platelet derived growth factor receptor.

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0165-5876/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijporl.2013.08.008

left facial itching and flushing intermittently. She denied any associated difficulty with breathing, speech, or swallowing. On physical examination she was found to have marked left facial hypertrophy involving the lower two thirds of the face. The fatty lesion did not seem to extend to the temporal or cervical regions. There was mild bony hypertrophy of the frontotemporal scalp on the affected side. She was also found to have isolated paresis of the buccal branch of the left facial nerve; this was reported to have presented and have been stable since a prior surgical procedure several years earlier.

Computed tomography (CT) and magnetic resonance (MR) imaging were obtained. CT demonstrated a diffuse, hypoattentuating lesion involving the left cheek and face. No encapsulation was visible and the lesion appeared to involve the left parotid gland, masseter and facial musculature, and the zygomatic arch. An iatrogenic fracture of the left zygoma was also noted (Figs. 1 and 2). On MR T1 imaging, the lesion was found to be hyperintense; consistent with the fatty nature of this condition.

The patient was restarted on a broad spectrum anti-angiogenic agent (thalidomide). Celecoxib was utilized perioperatively, in order to mitigate anticipated post-operative inflammation. Subtotal surgical resection was performed utilizing a parotidectomy incision. Extensive resection of the subcutaneous soft tissue was performed in conjunction with a superficial parotidectomy and complete facial nerve dissection through the distal branches. Concurrently a static sling procedure was performed in order to address the patient's buccal nerve palsy; and a nasolabial incision was made to excise redundant skin and address a ptotic left upper lip. The location of the main trunk of the facial nerve was tagged with prolene and a layer of inverted alloderm matrix was placed to maintain a plane for finding the facial nerve if any future revision were needed as well as for the prevention of Frey's syndrome [8].

Examination of the surgical pathologic specimen demonstrated c-kit and platelet derived growth factor receptor (PDGF-R) oncogene expression. A personalized, targeted chemotherapy regimen was devised in conjunction with the Department of Hematology/Oncology at Floating Hospital for Children. Thalidomide was discontinued and instead imatinib was initiated. The

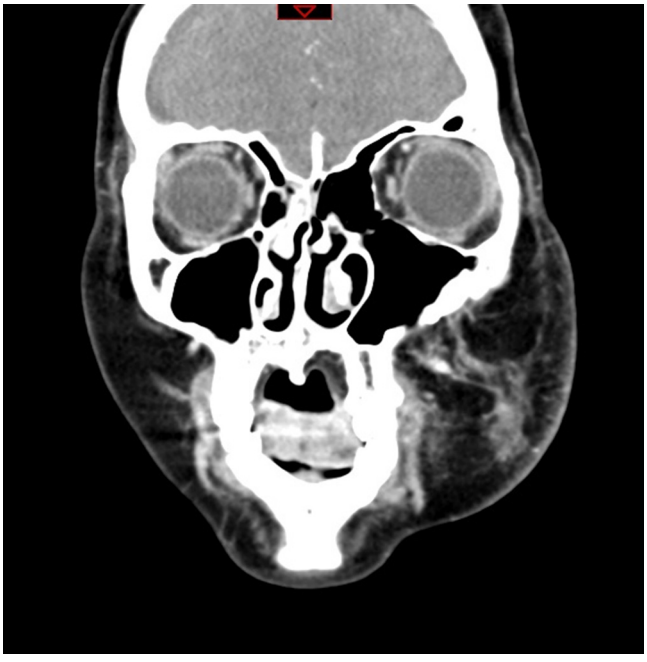

Fig. 1. Coronal CT of the face with contrast demonstrates a diffuse, hypoattenuating lesion involving the left face. Bony hypertrophy of the left facial skeleton is also present.

Fig. 2. Axial CT of the face with contrast demonstrates involvement of the left parotid gland and masseter muscle.

anti-inflammatory therapy with celecoxib was continued for 6 weeks post-operatively. The patient had an uncomplicated post-operative course and demonstrated significantly improved facial symmetry at follow up visits. At 18 months no clinical evidence of disease progression was evident (Figs. 3 and 4).

3. Discussion

The conventional management of CIL is with surgical excision [1,3–5,7]. The location of this lesion generally makes complete excision impossible and, as such, multiple subtotal resections are generally performed [1,4,6,7,9]. Controversy has existed regarding early intervention versus delaying care until maturation of the facial bony skeleton. Historically, early aggressive wide local excision was advocated [10]. However, current management generally involves minimally invasive interventions throughout childhood dependent on the independent needs of the patient and family. More extensive surgical procedures are delayed until early adulthood if possible [4,7].

The underlying pathophysiology of CIL is not well understood. Currently no known hereditary basis has been shown, although some authors have postulated an underlying germ-line mutation [2]. Regardless of an underlying propensity, the lesion of CIL itself is generally considered to be secondary to a somatic mutation at some point in early development [4]. In the case presented, the lipomatous tissue was found to express c-kit and PDGF-R. These two cell surface proteins are well characterized proto-oncogenes.

C-kit (or CD117) is a cell surface protein with tyrosine kinase activity that regulates cell cycle progression in response to cytokine stimulation (c-kit ligand). PDGF-R, the platelet-derived growth factor receptor, also represents a cell surface protein associated with an intracellular tyrosine kinase domain. Both c-kit and PDGF-R modify cell growth, mitosis, and angiogenesis (PDGF-R) through similar intracellular signaling pathways. Both of these surface receptors utilize an ABL type tyrosine kinase intracellular domain. Imatinib is a synthetic molecule that competitively inhibits ABL-type tyrosine kinase activity semi-competitively by binding to the enzyme's ATP binding site.

Fig. 3. Pre-operative (left) and postoperative (right) appearance at 18 months following intervention. Frontal views demonstrate improved facial contour and symmetry.

Imatinib was famously designed to treat the BCR-ABL fusion protein of chronic myelogenous leukemia. However, this molecule is a competitive inhibitor of any protein with an ABL type tyrosine kinase. After surgical pathology demonstrated expression of c-kit and PDGF-R, the patient's chemotherapeutic regimen was changed to a personalized, targeted therapy. Thalidomide was discontinued, and imatinib therapy was initiated. Imatinib is generally well tolerated with allergic reactions, weight gain, headaches and nausea the most common adverse effects [11].

It is the experience of the senior authors that CIL often undergoes a rebound increase in growth rate immediately after surgical resection. It is hypothesized that this response is secondary to pro-inflammatory signaling in response to traumatic lysis of adipose cells, as well as general surgical trauma. Celecoxib was used in the perioperative period with the goal being to minimize this inflammatory response and rebound growth period. Thalidomide has been found to be effective in the treatment of multiple myeloma through its mechanism as an antiangiogenic agent [12]. Since this discovery, it has been applied to a diverse group of diseases including glioblastoma multiforme, Hodgkin's lymphoma, and prostate cancer [13–15]. The use of these medications in CIL has not previously been reported.

Traditional management of CIL with surgical resection alone leads to recurrence rates as high as 62.5% [9]. Complete surgical excision is generally not possible given the proximity to the facial nerve. A combined medical and surgical approach to these lesions may limit the number of surgical interventions and patient morbidity. CIL is exceedingly rare, however, utilizing a personalized chemotherapeutic regimen allows for disease targeted treatment.

Fig. 4. Pre-operative (left) and postoperative (right) appearance at 18 months following intervention. There is facial nerve paresis in the buccal branch distribution, which was present preoperatively. Note the preservation of all preoperative facial nerve function, as well as improved upper lip excursion owing to upper lip suspension with static sling.

This interdisciplinary approach to treatment of CIL represents a completely new paradigm. Current algorithms advocating surgical management alone lead to unacceptably high rates of recurrence and potential morbidity. This is the first published case of applying personalized, targeted chemotherapy to the management of CIL. Combining surgical and medical intervention may allow for a synergistic approach to controlling this rare disease.

Financial disclosure

No external funding was secured for this study. The authors have no relevant financial relationships relevant to this article to disclose. Dr. Andrew R. Scott is a paid consultant for Advance Medical—medical second opinions. The authors have no conflicts of interest to disclose.

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