CASE REPORT

Surgical trauma induces overgrowth in lower limb gigantism: regulation with use of rapamycin is promising

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SUMMARY

We describe an unclassified overgrowth syndrome characterised by unregulated growth of dermal fibroblasts in the lower limbs of a 35-year-old woman. A *PIK3CA* gene mutation resulted in lower limb gigantism. Below the waist, she weighed 117 kg with each leg measuring over 100 cm in circumference. Her total adiposity was 50% accounted for by her legs mainly. Liposuction and surgical debulking were performed to reduce the size of the limbs but had exacerbated the overgrowth in her lower limbs. Systemic sepsis from an infected foot ulcer necessitated treatment by an above-knee amputation. Postoperatively, the stump increased in size by 19 kg. A trial of rapamycin to reverse the growth of the stump has shown promise. We discuss the clinical and genetic features of this previously unclassified disorder and the orthopaedic considerations involved.

BACKGROUND

Overgrowth syndromes are characterised by unregulated cellular growth leading to proportionate or disproportionate enlargement of certain body parts or the entire body. They are rare disorders and are associated with an increased risk of malignancy.¹ We describe a novel overgrowth syndrome leading to gigantism of the lower limbs. The patient presented to our tertiary combined orthopaedic and plastic (orthoplastic) surgery service with septicaemia from an infected foot ulcer. An above-knee amputation was indicated to control sepsis which had not, until surgery was undertaken, been achieved despite antibiotics. Surgery was complicated by the size of the limb and a rebound growth of the stump postoperatively. We discuss the genetic findings behind this newly discovered syndrome as well as the surgical considerations of this condition.

CASE PRESENTATION

Background

At birth, the patient was found to have enlarged lower limbs disproportionate to the remainder of the body. The left foot had an equinovarus deformity and the right foot resembled a hand. During childhood, the patient developed a 4-inch leg length discrepancy and a fixed scoliosis (figures 1 and 2). When aged 15 years, gangrene of the distal portion of the fifth toe on the right foot developed secondary to an infected wound and resulted in autoamputation. This toe grew back

twice its original length. There were coincident problems of recurrent lower limb cellulitis, insulin resistance without diabetes mellitus, protein S deficiency causing thromboembolism, gastritis with vitamin B₁₂ and iron deficiency treated with ferrous sulfate, a hypoplastic right kidney, a large bladder diverticulum, mitral valve reflux and severe bilateral hip osteoarthritis. Lumbar-sacral nerve neurofibromas lead to urinary incontinence and a peroneal nerve palsy. The family history was unremarkable.

X-rays (figures 3–5) of her limbs prior to amputation showed gross distorted anatomy bilaterally with severely arthritic knee joints, dysplastic and degenerate hips and disorganisation and overgrowth of bone as well as Charcot-like changes in the joints. A full body MRI scan revealed a complete absence of subcutaneous fat in the upper limbs, face, neck and entire thoracic wall (except for breast tissue). The left anterolateral and posterior abdominal walls were bereft of fat, whereas the right anterolateral abdominal wall has a very thick layer (figure 6). There were thickened and tortuous right and left sciatic nerves and multiple left lower limb soft tissue nodules. There was extensive fat in the subcutaneous and intermuscular layers in both of the lower limbs (figure 7), bilateral varicose veins and ankylosis in multiple lower limb joints.

Below the waist, the patient weighed 117 kg with leg circumferences of over 100 cm. A dual energy X-ray absorptiometry scan demonstrated that her total adiposity was 50% due to her lower limbs.² Attempts at surgical reduction of the limbs by liposuction and surgical debulking induced an accelerated overgrowth of the lower limbs.

At 32 years of age, this patient presented to her local hospital with septicaemia secondary to an infected ulcer of the left foot (figures 8 and 9). Control of sepsis was unsuccessful despite intensive care admission, early local debridement and administration of intravenous piperacillin/tazobactam. She was transferred to a tertiary orthopaedic unit for further management. A decision to control sepsis through an above-knee amputation was taken. The procedure was undertaken as a combined orthoplastic endeavour (figure 10). Three assistants were needed to handle the limb during the procedure. A suitable tourniquet was unavailable due to the size of the limb and the use

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Figure 1 This patient as a child. Her lower limbs are disproportionately larger than the rest of her body.

Figure 2 This patient as an adult. The lower limbs have continued to grow in a disproportionate fashion.

of an Esmarch bandage as a tourniquet applied ([figure 11](#)). This was abandoned during the procedure due to the tourniquet being ineffective; consequently, a transfusion of 6 units of packed red cells was needed for intraoperative blood loss.

Anteroposterior fasciocutaneous flaps were created. A difficult dissection revealed a deep subcutaneous layer, massive hypertrophy of cutaneous and sciatic nerves, fatty replacement of the muscles of the thigh, a knee joint with gross aberration of the anatomy and ossification within the distal quarter

Figure 3 Plain AP X-ray of the left knee showing extensive joint degeneration and calcification of quadriceps muscles. AP, anteroposterior.

Figure 4 Plain X-ray of the right hip showing dysplasia and destruction.

of the quadriceps muscle bulk. Neurovascular structures were ligated and divided. The knee joint was disarticulated followed by an osteotomy of the distal femur and calcified distal quadriceps muscle. The limb was sent to pathology and samples from the ulcer were sent to microbiology. The anterior and posterior stump flaps were closed over with insertion of two deep suction drains.

Figure 5 Plain X-ray of the right ankle with distorted anatomy.

Figure 6 Abdominal MRI demonstrating vast amounts of subcutaneous fat in the right abdominal wall and absence of fat in the left abdominal wall.

INVESTIGATIONS

Pathology

The amputated limb was 28 kg in weight, 80 cm in length and 35 cm in diameter. There was widespread dermal fibrosis and fatty replacement of the muscles of the leg ([figure 12](#)). Severe osteoarthritis was seen in the knee joint. Microscopic examination revealed a normal epidermis with an increase in dermal thickness due to increased collagen formation and oedema.

The knee joint had extensive osteoarthritic changes with reactive fibrous and fibrocartilaginous proliferation and osteophytosis. Thickened trabeculae within bone were of normal structure and the marrow contained normal haematopoietic tissue.

Figure 7 Left thigh MRI demonstrating aberrant anatomy and extensive fibroadipose and muscle atrophy.

Figure 8 The infected foot ulcer on the left foot.

Genetics

Lindhurst *et al* performed whole exome and Sanger sequencing of DNA from lower limb dermal fibroblasts, which confirmed two mutations: (1) the herterozygous *PIK3CA* mutation c.3140A>T (rs121933279, which predicts p.His1047Leu) and

Figure 9 The right foot resembles a hand.

Figure 10 Closure of the flaps with osteomyodesis of the deep muscles.

Figure 11 Anteroposterior fasciocutaneous flaps were created and deep dissection to ligate vascular trunks.

Figure 12 Histology slide from the leg demonstrates extensive adipocyte and fat infiltration.

(2) *USHBP1* c.280c7G (which predicts p.Glu94Gln). However, the literature did not suggest an association between *USHBP1* mutations and our patient's phenotype and was thus not studied further. A graph of the *PIK3CA* mutation can be found in Lindhurst *et al*'s original paper.²

OUTCOME AND FOLLOW-UP

Intravenous piperacillin–tazobactam and oral ciprofloxacin were administered postoperatively after *Enterococcus* was grown from intraoperative tissue cultures. Phantom limb pain was successfully treated with pregabalin. Prosthetic fitting was achieved initially but a change in size of the amputation stump (leading to an increase in total body weight of 19 kg) affected prosthesis fit and significantly hindered rehabilitation (figure 13). Translational research on the aberrant gene pathway identified pharmacological targets amenable to drug therapy. The result of a

Figure 13 The patient postoperatively with continued overgrowth of her stump.

trial of rapamycin in this patient to reverse the growth of the stump has been encouraging. Our patient has taken 1 mg of rapamycin once per day since 2013, which has caused cessation of overgrowth, regression of affected areas and a reduction in the size of the stump. The patient's weight and stump circumference were used to measure the effects of rapamycin. Our patient has a current height of 5'4 and a weight of 101.5 kg. She has lost a total of 33.5 kg and the circumference of the stump has reduced from 110 cm to 95 cm.

DISCUSSION

Overgrowth syndromes are characterised by a dysregulation of cellular growth leading to tall stature or enlargement of certain body parts. The presentation is variable due to the number of molecular growth factors and the complexity of processes involved in growth. A multidisciplinary approach is required together with genetic counselling.¹

This patient's condition was misdiagnosed as Proteus syndrome (PS).³ PS is an extremely rare type of overgrowth syndrome characterised by mosaic genetic anomalies resulting in rapid and asymmetric tissue growth.⁴ It affects men more frequently than women.⁵ Tissues most commonly involved are fat, connective tissue and bone.⁶ However, multiple visceral involvement including central nervous system, bowel, spleen and thymus have also been reported in the literature.⁷ Klippel-Trenaunay syndrome (KTS) is a rare congenital vascular disorder and was another diagnostic possibility. However, our patient lacked the lateral venous anomaly and port wine stain characteristic of this condition.² CLOVES syndrome is another rare overgrowth syndrome, which differs to our case in that our patient lacked the vascular anomalies and verrucous epidermal naevi typical of this condition.³

The most recent clinical and genetic evaluation of this patient has revealed an unclassified overgrowth syndrome. Lindhurst *et al* reported a somatic activating mutation of the *AKT* gene is the cause of overgrowth seen in PS. The *AKT* gene is an oncogene and plays a significant role in cell division and apoptosis.⁸ Tissue samples from this patient were genetically analysed to reveal a mutation in the *PIK3CA* gene.² This is in contrast to a mutation in the *AKT* gene causing PS. *PIK3CA* encodes one of the subunits for the PI3K protein and promotes cell growth.² Dysregulated cell growth ensues when *PIK3CA* undergoes an activating mutation. PI3K is a key member of the RTK/PI3K/AKT pathway which is upregulated in solid tumours.² *PTEN* is a tumour suppressor gene and negatively regulates PI3K. An inactivating mutation of *PTEN* was originally thought to be the cause of PS.⁸ The clinical manifestations of overgrowth syndromes vary widely despite the close relation of *PIK3CA* and *AKT* in cellular growth. Kepler-Nouriel *et al*⁹ have proposed clinical features for diagnosis and criteria for further testing in *PIK3CA* overgrowth syndromes. The presence of a *PIK3CA* mutation does not correlate with a diagnosis of PS.

Lindhurst *et al*² described nine other patients (in addition to this patient) who had a *PIK3CA* mutation and were incorrectly diagnosed with PS. All patients had a wide range of severity and natural history of clinical features. Common to them were progressive segmental overgrowth of subcutaneous, muscular and visceral fibroadipose tissue with skeletal overgrowth. Some patients presented with minor overgrowth isolated to one thumb whereas others experienced more severe overgrowth of the trunk and lower limbs. Eight of the 10 patients have undergone orthopaedic procedures to manage the overgrowth and none have developed malignancy.

A unique feature of this patient's condition was trauma, including surgery, accelerated overgrowth in the lower limbs. This is in contrast to the other patients reported in Lindhurst *et al*'s case series who have been successfully treated with surgery. A trial of rapamycin chosen on the basis of its mechanism of action and success in treating tumours associated with AKT/PI3K upregulation has been encouraging and prompts further analysis of this agent. Rapamycin is a macrolide that was originally developed as an antifungal before it was found to have immunosuppressive and antiproliferative effects. It is used regularly for treating rejection in renal transplantation¹⁰ and for coronary stent coating.¹¹ Rapamycin blocks AKT signalling by binding to mammalian target of rapamycin, thereby inhibiting phosphorylation of downstream targets. This pathway is commonly upregulated in certain cancers and its use in oncology is also increasing. Side effects include lung toxicity, tumour development and insulin resistance.

Learning points

- Greater research is needed on this condition and the *PIK3CA* gene.
- It is not known why the cells affected by this mutation divide rapidly when subjected to surgical trauma.
- This patient has a *PIK3CA* genetic mutation and has highlighted two important features to surgeons called to deal with such overgrowth syndromes: first, fibroadipose cells undergo accelerated overgrowth when subjected to surgical trauma; second, rapamycin may prove to be a suitable treatment for overgrowth caused by *PIK3CA* mutations.

Contributors RSP was responsible for researching the topic and writing the final paper. WDH was responsible for editing the paper. KG was a senior editor of the

paper. DN was responsible for planning the paper, provided a senior opinion as editor for the paper and should be regarded as the guarantor for the overall content of the paper.

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