Giant elephantiasis neuromatosa: a proposal for the role of primary lymphatic drainage anomalies in the setting of Neurofibromatosis type 1.

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Abstract

Background: Elephantiasis neuromatosa (EN) can arise from a plexiform neurofibroma of both superficial and deep nerves developing from a hyperproliferation of the perineural connective tissue infiltrating adjacent fat and muscles. To date, the clinical association between EN and NF1 has been poorly defined especially regarding the role of the lymphatic alterations and the consequent lymphedema. Methods: Lymphedema and limb lymphatic assessment were performed for the proband. NF1 germline mutations assessment were achieved in the proband and her father. The lower limb lymphatic assessment was also performed for a NF1 gene-carrier proband with clear-cut NF1 diagnostic criteria in the absence of limb lymphedema and/or other lymphatic disorders. Result: Case presentation: We report the clinical and biomolecular features of EN arisen in a NF1 patient with clear clinical diagnostic criteria: multiple café au-lait macules, neurofibromas, EN, positive family history and novel NF1 germline c.1541_1542del. Lymphoscintigraphy allowed us to accurately investigate lymphatic anomalies highlighting a marked dermal backflow in the affected limb, a hypertrophy of the ipsilateral inguinal and external iliac lymph nodes and a bilateral lower limb lymph flow delay. These data support the hypothesis that an extensive hyperproliferative process involving perineural connective, limb soft tissues, bones and lymphatic system can be responsible of EN in NF1 patients, based on adipocyte metaplasia triggered by lymphostasis and lymphedema and bone overgrowth and gigantism cased by chronic hyperemia. Conclusions: A synchronous onset of lymphatic anomalies and of cutaneous/subcutaneous and bone involvement may allow an early diagnosis of EN in NF1 pediatric patients before the full expression of this peculiar phenotype. Lymphoscintigraphy and MRI can be efficacious tools in the diagnosis and clinical characterization of early onset cutaneous, subcutaneous and skeletal anomalies allowing the detection of details that wouldn’t be visible with traditional radiograms and enabling a deepened anatomical study together with a pre-operative assessment.
**Keywords:** NF1, Elephantiasis neuromatosa, plexiform neurofibroma, mixoglioma gelatiniforme, primary lymphatic drainage.

**Background**

NF1 (MIM# 162200), also known as von Recklinghausen disease or peripheral neurofibromatosis, is one of the most common autosomal dominant disorders, with virtually 100% penetration in adulthood [1]. The prevalence of NF1 is about 1 in 3,500 people [2]. Diagnosis is based on the clinical criteria recommended by a NIH Consensus Conference [3], including multiple café au-lait spots (CLS), cutaneous or subcutaneous neurofibromas, plexiform neuromas, axillary or inguinal freckling, optic gliomas, and iris Lisch nodules.

Neurofibromas in NF-1 include the more commonly found "simple" neurofibromas, diffuse neurofibromas and plexiform neurofibromas, the most characteristic lesions of the disease. Plexiform neurofibromas are unencapsulated, poorly circumscribed tumors that diffusely infiltrate the nerves and the adjacent fat and muscles and contain a mixture of Schwann cells, fibroblasts, reticulin and collagen fibers and a loose mucoid matrix interspersed between the axons of the parent nerve [4]. The connective overgrowth can be limited to a single nerve or a plexus; in the latter case, when the plexus spreads to the epidermal and dermal tissues, it appears as a soft fibrous tumor, known as molluscum fibrosum, which can be multiple, covering all body sites (forehead, temple, eyes, nape, upper lip) with the exception of palms and soles [5]. Similarly, the plexiform neurofibroma variant, known also as mixoglioma gelatiniforme, is usually soft and is located in lower third of the leg [6]. A further dysplastic skin dysplasia associated with NF1 is pachidermocèle or dermatolysis which is characterized by an overlap of skin layers in the thorax, buttocks and limbs’ roots.
A large plexiform neurofibroma can involve an entire limb, and, when associated with lymphangiomatosis, it can give rise to a peculiar condition known as elephantiasis neuromatosa (EN) characterized by abnormal soft-tissue hypertrophy and bone dysplasia together with an early and excessive bone growth of the affected leg as compared to contralateral leg.

Lymphangiomatosis is a disorder characterized by diffuse or multifocal proliferation of complex, irregular lymphatic channels, involving soft tissue, viscera, retro-peritoneum, eyes, and the skeletal system [7,8]. The etiology of the disease is not yet fully understood, but the association of primary lymphatic dysplasia with a lymphatic proliferative process has been proposed [9]. A definitive contribution to diagnosis is made by lymphoscintigraphy, a non-invasive, effective and safe technique in determining the functional status of peripheral lymphatic vessels and nodes, which represents the favored diagnostic investigation for peripheral lymphedema [10,11].

Although some reports have described EN in NF1, the clinical association between EN and this genetic disorder has been poorly characterized and little is known about the role of lymphatic anomalies and the molecular basis underlying lymphedema development in NF1 associated-EN.

We present here a case of NF1 associated EN with typical clinical manifestations. The major aim of this report consists in a complete investigation of lymphatic and soft-tissue alterations related to the genesis of EN in a NF1 affected patient.

Methods

Lymphedema and limb lymphatic assessment
Limb circumferences were assessed with a common tape. Reference circumferences for the leg were the popliteal crease, point "zero" (K), +30cm (A), +20cm (B), +10cm (C) in the thigh, -10cm (D), -20cm (E), -30cm (F) in the lower leg, and 10 cm proximal from the tip of the first toe (G). Using these measurements, leg volumes were calculated [12].

Lymphoscintigraphy (LS) was performed to assess lower limb lymphatic function injecting 37 MBq 99mTc-labeled human serum albumin. Injection points were in the first, second and fourth interdigital and retromalleolar space of both the affected and contralateral foot. Image acquisition was obtained after 60 and 240 minutes using a dual head gamma camera (Philips Medical Systems) equipped with a low-energy and high-resolution collimator and energy peak centered on 140 KeV (window of 20%).

The criteria to define lymphatic dysfunction include delay, asymmetric or absent visualization of regional lymph nodes, and the presence of "dermal backflow." Additional findings include visualization of asymmetric lymphatic channels, collateral lymphatic channels, interrupted vascular structures, and lymph nodes of the deep lymphatic system (i.e., popliteal lymph nodes after web space injection in the lower extremities) [13].

The lower limb lymphatic assessment was also performed for a NF1 gene-carrier proband (after written informed consent) with clear-cut NF1 diagnostic criteria in the absence of limb lymphedema and/or other lymphatic disorders.

**Germline mutation analysis of NF1 gene**

Genomic DNA was extracted from the peripheral blood of patients with neurofibromatosis type 1 (NF1) using the QIAamp DNA Blood Mini Kit (Qiagen Inc., Valencia, CA, USA), and stored at
20°C until use. All of the NF1 exons were amplified by PCR with intron-spanning primers as described by [14] and analyzed with denaturing high-performance liquid chromatography (DHPLC) as described elsewhere [15]. For each abnormal elution profile, genomic DNA was directly sequenced in both directions using a CEQ Dye Terminator Cycle Sequencing Kit (Beckman Coulter Inc., Miami, FL, USA) according to the manufacturer’s protocol. Mutations were checked using the Mutalyzer program (http://www.LOVD.nl/mutalyzer).

**Results Case presentation**

Following, we report the case of a female patient brought to our attention because of a 29-year history of several neurofibromas and multiple (>6) café-au-lait macules. The patient presented with giant elephantiasis of the right leg, which started to grow during the late childhood, and accelerated its expansion in the following years (Figure 1).

At birth she showed a café-au-lait macule on the right thigh. By age 1, she developed a semi-liquid mass at the same site. The lesion were noticed by the parents and showed an indolent growth with no signs of bleeding or pain. At the histopathological examination, it showed the aspects of a lymphangioma. Lymphedema of the ipsilateral foot and discrepant leg lengths were noted successively.

In the following years, the leg growth was associated to bone proliferation, which required many osteotomies aiming at a stop of the growth. Two CNS hamartomas of the pallidus nucleous were also identified by MRI. Personal history and 3D-CT revealed mild lombo-sacral meningocele, giant L4 neurofibroma and significant scoliosis (Figure 3). Her family history was suggestive for NF-1
since her father had macrocephaly, hypertelorism and multiple *café-au-lait* macules and neurofibromas.

Genetic testing was performed in 2013, after the patient was referred to our department for genetic assessment. NF1 germline deletion g.129042_129043delAG; c.1541_1542del; p.(Gln514Argfs*43) was found in the proband and her father. At the best of our knowledge, this type of mutation has been described for the first time.

**Lymphoscintigraphic evaluation**

Conventional lymphoscintigraphy was performed to assess the lower limb lymphatic drainage pathway. Images obtained 60 minutes after the injections showed bilateral lower limb lymph flow delay. Mild dermal backflow in the absence of tracer migration was observed in the affected lower limb, while one inguinal LN was evidenced in the left limb. Posterior images confirmed the findings, also visualizing a popliteal LN in the healthy (left) leg.

Images acquired at 240 minutes showed significant dermal backflow in the right limb and hyperplasia and hypertrophy of the inguinal and external iliac LN, in comparison to the left ones.

In the healthy leg, popliteal and inguinal LN drainage was confirmed, while a mild dermal backflow was noticed (Figure 2a).

The MRI (Magnetic Resonance Imaging) and 3D CT (Computer Tomography) scan study showed a preponderance of adipose tissue in the elephantiasic limb, correspondent to 3/4 of its whole volume, in addition to a severe dorso-lumbar-sacral scoliosis with convexity on the left. The thickening of cutaneous and subcutaneous tissue of the leg was principally due to the presence of abundant adipose tissue within the muscle, resulting in a poor and atrophic muscle component with normal
vascular pattern and multiple serious venous ectasia. The remaining part of the affected limb was
composed by isolated groups of soft-tissue and highly-vascularized neurofibromas, mainly localized
on the dorsum of the foot, on the left ankle (10 cm diameter), on the dorsal part of the leg (4 cm
diameter), on the right iliac crest (5 cm diameter), on the medial side of the knee, on the thigh and
on nerve pathways at the level of L2 and in the paravertebral region near L5-S1 roots. (Figure 3).

Lymphoscintigraphic evaluation of another NF1 gene-carrier proband revealed a bilateral lower
limb lymph flow delay and in the absence of clinical lymphedema (Figure 2b).

Discussion

Elephantiasis neuromatosa is a rare clinical manifestation enclosed in the NF1 phenotype. It should
be defined as an early and excessive growth in width and length of the affected limb due to a
neoplastic proliferation of the perineural connective tissue together with a congenital lymphatic
insufficiency and chronic hyperemia. Actually, no more than 30 cases are described in the literature
(Table 1), although, the real incidence is estimated to be higher. The clinical expression is
characterized by plexiform neurofibromas located in the superficial or deep nervous system
associated with congenital lymphangiomathosis. Signs usually appear during the first years of life,
both due to lymphostasis and subsequent lymphedema causing adipocyte metaplasia of the adjacent
tissues and chronic hyperemia inducing bone overgrowth and focal gigantism [126].

Distinct superficial dysplastic skin alterations known as pachidermocele or dermatolysis,
histologically corresponding to mixoglioma gelatiniforme, must be distinguished from EN in
patients affected by NF1 [5].
To date, little evidence is available regarding the role of lymphatic alterations in the pathogenesis of EN.

However, considering other syndromic diseases clinically overlapped with NF1 (Table 2) we can hypothesize the role of lymphoangiogenetic regulator for the NF1 gene as already demonstrated for VEGFR3, FOX, PARP etc.

Primary or hereditary lymphedema (PL), associated with genetic changes leading to the misregulation of lymphatic function, may occur as the only clinically apparent anomaly or may occur as an expression of more complex inherited disorders, with both an autosomal or recessive pattern of inheritance (Table 2). There are three subtypes of hereditary lymphedema: primary congenital lymphedema (PCL) which presents at birth, praecox lymphedema which manifests during childhood, and late lymphedema that occurs in adults [137,148].

Histologically, primary lymphedemas are classified as aplastic, hypoplastic, hyperplastic and lymph-node fibrosis [159]. The heterogeneous phenotype of lymphatic system abnormalities in primary lymphedema may result from events occurring at different stages of the embryonic development of the lymphatic system [16,17 20,21].

The clinical manifestations in our case underlines the key role covered by lymphatic alterations.

Lymphoscintigraphy showed a marked delay in the lymphatic drainage of the limb affected by elephantiasis and a synchronous mild delay in the contralateral limb determining a condition of subclinical edema. MRI displayed a prevalence of adipose tissue in the limb with elephantiasis.

There are no studies on the pathogenesis of lymphangiomas in NF1 related EN. Landing and Farber classified lymphangiomas into 3 histological categories [18 22]: among these, capillary or simple...
Lymphangiomas are composed of capillary, thin-walled lymphatic channels; capillary lymphangiomas usually occur in the skin, but have also been reported in the bone and are considered as neoplastic. Malignant transformation and growth to elephantiasic dimension are complications less commonly reported [19,20,23,24].

Important data emerged from LS: severe dermal backflow in the affected limb was accompanied by hyperplasia and hypertrophy of the inguinal and external iliac LN, in comparison to the contralateral site; in the asymptomatic left lower limb, lymph flow delay was unexpectedly assessed 60 minutes after the injection, and later images confirmed a mild dermal backflow, providing evidence of lymphatic abnormalities also in the absence of clinical lymphedema (Figure 2a).

Inguinal lymph-nodal hypertrophy was already described in 3 cases studied by radionuclide lymphoscintigraphy, which showed dilated lower limb lymphatic channels and enlarged lymph nodes. Enlarged lymph nodes with prominent filling defects were the main features reported by a positive contrast pedal lymphangiogram in one of these case reports [1,215].

Based on the bilateral lymphatic defect, the presence of a primary lymphatic disease in our NF1 patient can be hypothesized.

Although we detected a bilateral delay in limb lymphatic drainage also in a NF1 gene-carrier proband with clinically normal limbs (Figure 2b), we cannot consider the peculiar subclinical lymphatic disorders as specific for the NF1 syndromic setting because the above mentioned studies evaluated only the affected leg. A lymphatic dysfunction in the apparently healthy controlateral limb of patients with unilateral lower limb swelling.
It is reported and authors suggested that this 32% of patients, in whom clinical lymphedema appeared to be unilateral, had abnormal scintigraphy in the clinically normal limb [1,215]. Consequently, it is likely that many patients “labeled” as having secondary lymphedema have a pre-existing constitutional lymphatic weakness [226].

The primary lymphatic disease is probably supported by a dysplastic-hypertrophic condition as a result of a congenital alteration of the lymphatic network. The hyperplasia of lymphatic channels and drainage nodes is likely caused by an event occurring during lymphatic specification and budding, or at the stage of the formation of primary lymph sacs before the separation of lymphatic vessels and lymph-node development [237]. The lymphoscintigraphic examination can allow a high-quality characterization and can be used in future studies on wider case series to provide a more accurate description of pathognomonic lymphedemas in NF1.

The clinical progression of lymphedema can be divided into different stages: a first asymptomatic stage showed by lymphoscintigraphy, characterized by a delay in lymphatic drainage, other subsequent stages where edema becomes clinically evident through the fovea-sign. In this stage, there is an accumulation of the extracellular lymph turning into a fibrotic-adipose edema due to unknown mechanisms of adipocyte proliferation induction [248]. The clinical evaluation of this lymph to fat transition is also explored by evaluating Stemmer’s sign [259].

Regarding the lymph to fat transformation, it is known that lymphostasis due to both primary and secondary lymphedema determines the fat cell transformation resulting in hypertrophied adipose tissue. Several reports [26-29 30-33] suggest that lymphedema leads to adipose tissue accumulation and fibrosis.
The lymphatic system's role in immune cell trafficking and immune responses, its contribution to fat transport, distribution, metabolism and its implication in the pathogenesis of chronic intestinal inflammation is known [30,31,34-35]. The intestinal fat accumulation in Chron disease is an example of an inflammatory process that induces an accumulation of adipose tissue [326].

By contrast, the molecular mechanisms regulating the process of adipose hyperplasia and hypertrophy following lymphostasis are still unknown.

Probably inflammatory cells play an important role in the induction of the transition of the lymph into fat. Even macrophages play a key role in this process.

Some authors have underlined that the adipose tissue can become hyperplastic and hypertrophic; other authors think that kilomicrones and lipoproteins like VLDL could stimulate the adipogenesis that is present in the lymphostasis and in the lymphedema. We hypothesized that inflammatory cells could stimulate the transdifferentiation of the mesenchimal/stromal cells of the fat [337]. They could also stimulate the adipogenesis as a direct effect on the dormant staminal cells. Moreover, we think that this process is amplified in NF1 and in EN due to a primary lymphatic disorder which is at the base of the clinical manifestation induced by the plexiform neurofibroma growth. The evidence that adipose tissue can constitute more than 2/3 of the whole elephantiasic limb can lead to several interesting surgical approaches. In fact, in addition to traditional demolition surgery, it is possible to consider less invasive techniques; for example liposuction and liposculpture could be adopted for reducing the adipose tissue mass with a consequent potential recovery of limb function and improvement in quality of life.

Regarding the other clinical aspects, several cases of musculoskeletal involvement have been reported in NF1 patients: spinal deformity, congenital tibial dysplasia (congenital bowing and
pseudarthrosis), and disorders of excessive bone and bone tissue growth [34 8]. Elephantiasis
neuromatosa-associated bone dysplasia is frequently encountered secondary to chronic hyperemia
or as part of the mesodermal dysplasia [35 9]. Disparity in limb length, periosteal and endosteal
thickening were typically reported in association with soft tissue hypertrophy in NF1 patients
affected by EN of the lower extremity [36 40].

Klippel-Trenaunay-Weber syndrome is characterized by a chronic hyperemia together with arterial
and venous capillary and lymphatic alterations. It is also characterized by bone asymmetry and
dysplasia. An increase in blood flow may lead to hypertrophy of the juxtaepiphyseal cartilage. A
similar event can be observed in Gorham disease, a rare disorder of unknown etiology observed in
young patients and characterized by lymphatic proliferation in bones and surrounding tissues [41]
(Table 2).

**Conclusion:** The diagnostic criteria for NF can be improved and better characterized: the
introduction and application of new criteria based on a wider case series (elephantiasy neuromatosa,
focal gigantism, mixoglioma gelatiniforme, primary lymphatic disorder) can lead to the early
diagnosis of NF1, especially in pediatric patients, when the full phenotype is not yet expressed.
Lymphoscintigraphy and MRI can be efficacious tools in the diagnosis and clinical characterization
of early onset cutaneous, subcutaneous and skeletal anomalies allowing the detection of details that
wouldn’t be visible with traditional radiograms and enabling a deepened anatomical study together
with a pre-operative assessment.
The identification of biomarkers involved in the described lymphatic disease could imply the identification of targeted-therapies which could inhibit specific pathways involved in the pathogenesis of the abnormal proliferation of the cutaneous, soft and bone tissues.

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References


Figure legends

Figure 1. Clinical aspect of Elephantiasis Neuromatosa.

Figure 2. 2a: Conventional lymphoscintigraphy performed to assess the lower limb lymphatic drainage pathway: Images obtained 60 and 120 minutes after the injections showed bilateral lower limb lymph flow delay. 2b: Lymphoscintigraphic pattern of another NF1 gene-carrier proband revealed a bilateral lower limb lymph flow delay and in the absence of clinical lymphedema.

Figure 3. Severe dorso-lumbar-sacral scoliosis with convexity on the left and preponderance of adipose tissue in the elephantiasic limb, correspondent to 3/4 of its whole volume detected by 3D-CT scan and MRI.
<table>
<thead>
<tr>
<th>Sex</th>
<th>Age of onset</th>
<th>Proband affected regions</th>
<th>Family history</th>
<th>Clinical features</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>30 years/ At birth</td>
<td>Left limb</td>
<td>Grandmother (2000 minute cutaneous tumours and scattered subcutaneous swellings), mother (schondroplasia).</td>
<td>Gross elephantiasis neuromatosa of the left limb. Subcutaneous tumors scattered all over the body, a pachydermatome of the occipital scalp, cutaneous freckles. Hypopigmentation of mucous membrane of the mouth, and muddy hypopigmentation of the conjunctive.</td>
<td>Spiegel RL and Fernando MC, 1920</td>
</tr>
<tr>
<td>M</td>
<td>40 years/ At birth</td>
<td>Neck</td>
<td>His mother had type I neurofibromatosis (NF-I).</td>
<td>Elephantiasis neuromatosa of the neck. Asymmetry of the rib cage. Deformity of the cervical column, of the left leg and of the left clavicle.</td>
<td>Westcott RJ and Ackerman LV, 1947.</td>
</tr>
<tr>
<td>M</td>
<td>22 years/ Childhood</td>
<td>Chest wall and axilla</td>
<td>There was no particular familial history of neurofibromatosis.</td>
<td>Elephantiasis neuromatosa of extensively involved the chest wall and the axilla.</td>
<td>Lenson N, 1956.</td>
</tr>
<tr>
<td>F</td>
<td>42 years/ -</td>
<td>Right leg</td>
<td>The family history is free from the stigmata of neurofibromatosis or any other inherited disease tendency. Her mother had gastric carcinoma.</td>
<td>Soft irregular bluish end mottled mass involving the distal two-thirds of the right lower extremity. Cerebrovascular haemangioma with the consistency of a lipoma. Numerous femoral cysts.</td>
<td>Marcinko DE, 1982.</td>
</tr>
<tr>
<td>M</td>
<td>11 years/ 3 years</td>
<td>Left thigh</td>
<td>Not reported.</td>
<td>Two cases of elephantiasis neuromatosa and overgrowth of abnormal bones with subperiosteal haemorrhage. Subsequent rapid ossification resulted in residual diaphyseal widening after minor trauma.</td>
<td>Yaghmai I and Talalchir M, 1977.</td>
</tr>
<tr>
<td>F</td>
<td>9 years/ 2 years</td>
<td>Right leg</td>
<td>Not reported.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>4 years/ -</td>
<td>Right lower extremity</td>
<td>Eleven of his relatives have neurofibromatosis.</td>
<td>Elephantiasis neuromatosa involving the right lower extremity. Numerous café-au-lait spots on the lower abdomen and groin. The right lower extremity was longer than the left. Dilation of the medial lymphatic channels in the lower extremity and enlarged right Blas nodes.</td>
<td>Sly JR, Marshak RJ and Woods GA, 1981.</td>
</tr>
<tr>
<td>F</td>
<td>18 years/ At birth</td>
<td>Right haliux</td>
<td>No familial history of neurofibromatosis.</td>
<td>Only one large café-au-lait spot on the right haliux. Soft tissue hypertrophy with massive enlargement of both proximal and distal phalanges.</td>
<td>Harris WC, Jr, Alpert WF and Marciano DE, 1982.</td>
</tr>
<tr>
<td>F</td>
<td>17 years/ Childhood</td>
<td>Right gluteal sulcus</td>
<td>There was no predisposition to either familial or hereditary disorders.</td>
<td>Elephantiasis neuromatosa of the right gluteal sulcus, coexistent with lipomatosis.</td>
<td>Heök N, Młodyńska S, Dabrowska R and Lassen M, 1984.</td>
</tr>
<tr>
<td>F</td>
<td>30 years/ At birth</td>
<td>Left lower limb</td>
<td>Not reported.</td>
<td>Elephantiasis neuromatosa of the left lower limb maximal in the calf. Dysplastic bones of the left hemipelvis and leg with floral osseous situations. The skin of the thigh was loose and inelastic.</td>
<td>Birch PD and Davies AM, 1988.</td>
</tr>
<tr>
<td>M</td>
<td>13 months/ At birth</td>
<td>The right orbital</td>
<td>Not reported.</td>
<td>Buphthalmos. An enlarged optic canal, a fibrous dysplasia of the greater wing of sphenoid bone. Longer right orbita and a slight deformity of the vertebrae of the lumbar tract.</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>11 years/ At birth</td>
<td>The temporal and zygomatic</td>
<td>Not reported.</td>
<td>Facial elephantiasis without buphthalmos. Greater wing of sphenoid bone; right optic foramen larger than the left. Iris nodules, ectropion uveae, increased optic nerve cupping. Small neurofibromas of the zygomatic and temporal region.</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>34 years/ Since 8 years</td>
<td>Right limb and pelvis</td>
<td>His mother, grandmother, sister, nephews had neurofibromatosis.</td>
<td>Elephantiasis neuromatosa involving the right lower limb and pelvis, leading to a right hip disarticulation. Grossly enlarged lower limb complicated by infected dequities ulcers. A leg length discrepancy. (After surgery a large neurofibroma of the sciatic nerve).</td>
<td>Kuo LA and Kuo RS, 1990.</td>
</tr>
<tr>
<td>F</td>
<td>22 years/ At birth</td>
<td>Right foot</td>
<td>No family history of NF1 was presented.</td>
<td>Enlargement of the whole right foot with conspicuous gigantism of 2nd to 5th toes. The overlying skin was coarse, dry, thick. Overgrowth and elongation of all the bones of the foot (2nd and 3rd metatarsals and their phalanges). A huge soft tissue mass with no bone involvement.</td>
<td>Roy SM and Ghosh AK, 1992.</td>
</tr>
<tr>
<td>M</td>
<td>23 years/ At birth</td>
<td>Right foot</td>
<td>Not reported.</td>
<td>Gigantism of the right foot and elongation of all the bones of the foot (metatarsals and a huge soft tissue mass).</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>18 years/ Early Childhood</td>
<td>Right foot</td>
<td>His father had elephantiasis neuromatosa. One of his three brothers has few cutaneous nodules affecting the right lower limb only.</td>
<td>Gigantism of the right foot with swelling at the heel. Elongation of all the bones (metatarsals and a soft-tissue mass affecting mainly the hind foot).</td>
<td></td>
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<tr>
<td>M</td>
<td>6 years/</td>
<td>Right foot</td>
<td>No family history of NF.</td>
<td>Enlargement mainly of the forefoot and the swelling was more prominent between the prest and 2nd toe. No café-au-lait spots.</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>3 months/ At birth</td>
<td>Neck and back</td>
<td>Family history did not reveal occurrence of similar illness in any of members.</td>
<td>Congenital plexiform neurofibroma involving neck with elephantiasis neuromatosa with sarcomatous nodule. The skin covering the tumor was hairy, redundant and dark. The skin covering the nodule was thinned out and ulcerated.</td>
<td>Korkidakar HR, Vyas AS, Kumbhakara NR and Talota RJ, 1990.</td>
</tr>
<tr>
<td>F</td>
<td>33 years/ 6 years</td>
<td>Right leg</td>
<td>Family history of neurofibromatosis.</td>
<td>Elephantiasis neuromatosa of the right leg. Severe dysplasiasis in the right lower leg not confined to a single nerve.</td>
<td>Mintte F, Maizke M, Johannes S, Dietrich B and Dengler R, 1996.</td>
</tr>
<tr>
<td>M</td>
<td>20 years/6 years old</td>
<td>Left shoulder and arm</td>
<td>No family history of NF</td>
<td>Elephantiasis neuromatosa with Becker’s melanosis. Hairly and brown-black hyperpigmented patches on left shoulder, left upper back and left arm. Lisch nodules.</td>
<td>Akyol M, Orceli K, Mandilah M and Elagöz S, 1999.</td>
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<tr>
<td>M</td>
<td>35 years/6 years old</td>
<td>Right thigh and sacral region</td>
<td>Not reported.</td>
<td>A soft tissue mass and enlargement of the right upper leg.</td>
<td>Lorberboym M, Terje L and Lampl Y, 2000.</td>
</tr>
<tr>
<td>F</td>
<td>13 years/At birth</td>
<td>Left limb</td>
<td>Her mother had type I neurofibromatosis (NF-I).</td>
<td>Elephantiasis of the left leg with recurrent massive subperiosteal hematoma.</td>
<td>Steenbrugge F, Poffyn B, Uyttendaele D et al., 2001.</td>
</tr>
<tr>
<td>F</td>
<td>14 years/At birth</td>
<td>Right limb</td>
<td>Not reported.</td>
<td>Elephantiasis neuromatosa involving the right lower limb. Anemia and hepatitis B.</td>
<td>Martinez-Garcia S, Vera-Gasabo A, Elvy-Garcia Carusco C et al., 2008.</td>
</tr>
<tr>
<td>M</td>
<td>56 years/Childhood</td>
<td>Right leg</td>
<td>There was no particular familial history of neurofibromatosis.</td>
<td>A huge mass of elephantiasis neuromatosa in the right leg.</td>
<td>Hoshi M, Ieguchi M, Taguchi S and Yamasaki S, 2009.</td>
</tr>
<tr>
<td>M</td>
<td>15 years/Childhood</td>
<td>Right limb</td>
<td>No family history of NF-1 in first-degree relatives.</td>
<td>Elephantiasis neuromatosa of the right leg. Osteous abnormalities included thinning of bones, erosion of distal articular surfaces and periosteal dysplasia.</td>
<td>Bano S, Prasad A, Yadav SN et al., 2010.</td>
</tr>
</tbody>
</table>
Table 2. Inherited disorders with primary effects on lymphatics.

<table>
<thead>
<tr>
<th>Disorders (Inheritance)</th>
<th>Gene/Locus</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milroy’s disease or Nonne-Milroy-Meige syndrome (AD)</td>
<td>VEGFR3</td>
<td>Lymphedema in their lower legs and feet at birth or develop it in infancy, papillomas, prominent leg veins, hydrocele in males, some individuals develop cellulitis.</td>
</tr>
<tr>
<td>Lymphedema praecox or Meige disease (AD)</td>
<td>FOXC2</td>
<td>Lymphedema usually develop during puberty, absence of signs or symptoms affecting other parts of the body.</td>
</tr>
<tr>
<td>Hereditary lymphedema or Lymphedema Tarda (AD)</td>
<td>FOXC2</td>
<td>Lymphedema after the age of 35 and may involve the swelling of either one or both legs.</td>
</tr>
<tr>
<td>Lymphedema-distichiasis syndrome (AD)</td>
<td>FOXC2</td>
<td>Lymphedema of the limbs, distichiasis on both the upper and lower lids, related eye problems including astigmatism or scarring of the cornea, varicose veins, heart abnormalities, ptosis and a cleft palate.</td>
</tr>
<tr>
<td>Lymphedema and ptosis syndrome (AD)</td>
<td>FOXC2</td>
<td>Ptosis and lymphedema associated with lymphedema-distichiasis syndrome and Noonan syndrome.</td>
</tr>
<tr>
<td>The yellow nail syndrome (AD)</td>
<td>FOXC2</td>
<td>Yellow discoloured nails, lymphedema, rhinosinusitis, pleural effusions and bronchiectasis.</td>
</tr>
<tr>
<td>Microcephaly-lymphedema-chorioretinal dysplasia (AD)</td>
<td>KIF11</td>
<td>Chorioretinal dysplasia, myopic astigmatism, retinal dystrophy, optic atrophy, ptosis, hypotonia, congenital lymphedema, microcephaly, mental retardation and hair pattern anomalies.</td>
</tr>
<tr>
<td>Intestinal lymphangiectasia (AR)</td>
<td>-</td>
<td>Dilated intestinal lymphatics, hypoalbuminemia, protein-losing enteropathy, lymphocytopenia and edema.</td>
</tr>
<tr>
<td>Noonan syndrome (AD)</td>
<td>PTPN11, SOS1, RAF1</td>
<td>Short stature, heart defects, bleeding problems, skeletal malformations, reduced pubertal growth spurt, delayed puberty and infertility in males, vision or hearing problems and lymphedema.</td>
</tr>
<tr>
<td>Aagenaes syndrome or Cholestasis-lymphedema syndrome (AR)</td>
<td>FLT4</td>
<td>Congenital hypoplasia of lymph vessels, which causes chronic severe lymphedema (mainly of the legs but also on the hands, scrotum and periorbital soft tissues) and recurrent cholestasis in infancy, and slow progress to hepatic cirrhosis and giant cell hepatitis with fibrosis of the portal tracts.</td>
</tr>
<tr>
<td>Hennekam syndrome or Hennekam lymphangiectasia-lymphedema syndrome (AR)</td>
<td>CCBE1</td>
<td>Intestinal and renal lymphangiectasia, dysmorphic facial appearance, seizures and mental retardation. The facial features include hypertelorism with a wide, flat nasal bridge, epicanthic folds, small mouth and small ears.</td>
</tr>
<tr>
<td>Klippel-Trenaunay-Weber syndrome (most cases are sporadic, although a few cases are AD)</td>
<td>VG5Q</td>
<td>It comprises a triad of port-wine stain, varicose veins, and hypertrophy of the bones and overlying soft tissue. Asymmetrical capillary and cavernous hemangiomas on the trunk or limbs, arteriovenous fistulae, lymphedema, varicosities, asymmetrical hypertrophy and visceromegaly may be present.</td>
</tr>
<tr>
<td>Gorham-Stout syndrome (AR)</td>
<td>PDGFR, VEGFR</td>
<td>Lymphatic proliferation in bones and surrounding tissues. It is characterized by spontaneous and progressive destruction and resorption of one or more bones.</td>
</tr>
<tr>
<td>Neurofibromatosis type-I (AD)</td>
<td>NF1</td>
<td>Elephantiasis neuromatosa, multiple café-au-lait spots, neurofibromas, plexiform neurofibroma, freckling of the groin or the axilla, Lisch nodules, optic glioma, skeletal abnormalities.</td>
</tr>
</tbody>
</table>

AD: autosomal dominant; AR: autosomal recessive.
Additional files provided with this submission:

Additional file 1: foto[1].JPG, 2109K
http://www.biomedcentral.com/imedia/101387281127660/supp1.jpeg