Neurofibromatosis type 1: Surgical Perspectives

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Abstract

Introduction: Neurofibromatosis type 1 (NF1) affects about 1 in 3000 people. The indications for surgical intervention in patients with NF1 are not always clear-cut. In low-income economies, where scarcity of resources and skilled manpower often dictate levels of healthcare, a broad knowledge base of NF1 is required in order to adequately manage NF1 complications.

Materials and Methods: The authors performed PubMed/internet searches for articles on surgical aspects of NF1, as well as a review of the pathology department database for reports on all specimens submitted from patients with NF1 over a 16 year period. A retrospective chart review was performed on all patients with NF1 referred to the authors' institution for surgical intervention between January 2004 and January 2011.

Results: Forty five articles describing aspects of surgical care of patients with NF1 qualified for inclusion in the review. Pathological specimens were submitted from a total of 333 patients with NF1 between 1992 and 2008. These represented 0.4% of all submitted specimens during this period. The male to female ratio was 1.05:1; 9.3% of these specimens were reported as malignant peripheral nerve sheath tumors. Fifteen of sixteen NF1 patients referred to the institution for surgical intervention over a seven year period underwent an average 1.7 interventions. Most presented late, some with malignancies (27%), making it difficult to obtain good cosmetic and functional results. Three representative case presentations are reported from these patients to show that (i) NF1 complications affects any system, cannot be predicted, making prognosis uncertain, (ii) cervical spine instability, excessive intra-operative bleeding and post-operative edema are important peri-operative considerations, (iii) essential role of access to safe blood for transfusion and an intensive care service.

Conclusions: Surgical symptom control (cosmesis, function, and pain) rather than surgical cure is the primary, achievable goal of most interventions in patients with NF1. Lifelong surveillance is necessary for all NF1 patients to avert or minimize complications, and thus improve surgical outcomes.

Introduction

The term 'neurofibromatosis' includes neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2) and others (1,2). NF1 affects about 1 in 3000 people and has an autosomal dominant inheritance pattern with complete penetrance, variable expression, and a high rate of new mutation. Fifty percent of NF1 patients represent new mutations. An affected individual has a 50% chance of transmitting NF1 to each offspring (3).

A positive diagnosis of NF1 is based on two or more of the following: neurofibromas, café-au-lait macules, skinfold freckling, skeletal dysplasia, Lisch nodules, optic gliomas and a first degree relative with NF1(2). Localized, diffuse or plexiform neurofibromas can involve any organ in the body, resulting in varying degrees of deformities and/or dysfunction (3,4).

The psychological effects of these tumors are immense. Many affected patients are deprived of social integration, development and self actualization (5,6). Ostracized from society, children and adults with NF1 often live in poverty, hidden away only to present with advanced lesions (Figure 1).

A multi-specialty approach is required in the care of NF1 patients. Although not always clear-cut, broad indications for surgical intervention include functional improvement (pseudo-arthrosis, penile lesions Figure 2), cosmesis (orbito-temporal lesions Figure 3 and 4), and malignancy (malignant peripheral nerve sheath tumor - MPNST Figure 5) (7). Palliative debulking is an option when this may result in an improved quality of life (Figure 1). Goldberg et al. proposed a classification of NF1 patients that describes the threat to life, and can be used in long term patient follow ups in determining progression (Table 1).

A broad base of knowledge of NF1 is therefore needed for the surgical treatment of NF1 complications. This paper outlines the surgical pathologies in NF1 patients, their management, anticipated difficulties and possible solutions.

Materials and methods

An internet/PubMed search was performed on the terms 'neurofibromatosis type 1', 'neurofibromatosis type 1 + Africa', and 'surgery + neurofibromatosis type 1 + Africa'. Data on all patients with a diagnosis of NF1 from whom specimen had been obtained and submitted for histopathological examination were extracted. The authors also reviewed clinical data on all patients with NF1 referred to the hospital for surgical intervention, between January 2004 and January 2011. From these, three representative case presentations are made.

Results

There were 140 relevant publications retrieved from the internet/PubMed search: of these, only 45 were of surgical relevance.

From a database of over 75,000 specimens submitted between 1992 and 2008, there were 333 specimens from NF1 patients evaluated, representing 0.4% of total submitted specimen over this period. The male to female ratio of NF1 patients was 1.05 to 1. Histopathological examination revealed that 9.3% of the specimens were malignant peripheral nerve sheath tumors (MPNST).

A total of sixteen patients with NF1 were referred to the authors' institution for surgical intervention between January 2004 and January 2011; one patient was deemed not to require surgery. Their average age was 19 years, with a male to female ratio of 1.2 to 1. While 44% of the patients had a good surgical outcome, two patients considered their cosmesis 'fair' or acceptable (Figure 4). Five patients got lost to follow-up; some of these had been referred to an oncologist, but did not return for review. Twenty seven percent of the sixteen patients were found to have MPNST. Their average age was 24 years (Table 2). Thirteen percent of patients who had surgery had grade 1 lesions, 47% had grade 2 lesions, while 40% had grade 4 lesions. Their average ages were 17, 17.7 and 17.8 years, respectively.

Case presentations

Case 1

A 27 year-old male with a longstanding history of difficulty in walking. He had not been in contact with anyone outside his immediate family for two years. Six months prior to presentation, he had developed dyspnea at rest, with orthopnea. A clinical examination revealed large plexiform neurofibromas on all four extremities, multiple neurofibromas, café au lait spots, a macrocephaly and severe kyphoscoliosis (Figure 1). He was planned for an initial debulking of extremities to improve his mobility, and later thoracic surgery to debulk intrathoracic neurofibromas.

The limbs were debulked under tourniquet control. Four units of blood were transfused peri-operatively. Post-operatively he developed severe whole-body edema which improved towards the end of the first post-operative week. Attempts at extubating him were unsuccessful as he would desaturate, and a tracheostomy was performed to permit his weaning from the ventilator. After two weeks, he developed progressive pulmonary failure and died.

Case 2

An 11 year-old male with NF1 and a large left orbito-temporal plexiform neurofibroma and a pulsatile blind eye. He had never been to school, and could not play with other children because of this deformity (Figure 3). He underwent two debulking procedures before he was happy to mix with other children and go to school (Figure 4). A mesh was used to replace the subcutaneous fascia; intra-operatively he required a unit of blood. Mesh was also used to close the left orbital cavity after enucleation and replacement of dura into the cranium through the superior orbital fissure. After the initial operation he was taken to the intensive care unit (ICU) for the immediate post-operative recovery. Prolonged post-operative edema prevented extubation, necessitating a tracheostomy.

Case 3

A 35 year-old male with NF1 presented with abdominal pain, early satiety and a large abdominal mass. On examination, his entire body was covered with small neurofibromas. He had a tense abdomen with a palpable firm mass (Figure 5). A computerized tomogram scan revealed a large retroperitoneal tumor with para-aortic lymphadenopathy. There were no metastases in the liver, lungs or bones. He developed bowel obstruction just before his scheduled surgery. Tumor debulking with excision of tumor obstructing bowel was performed. He required intra-operative transfusion with five units of blood. He did not require ICU care post-operatively. Histological examination of the specimen revealed an MPNST. The patient recovered uneventfully and was referred to an oncologist for further management.

Discussion

Ramanjam et al. presented the first of few reports on NF1 phenotype in Africa, documenting findings consistent with Western literature (8,9). There are even fewer detailing surgical interventions from

Grade	Clinical complications	Threat to life
1 (Minimal)	Few NF1 complications that present no threat to the health of the individual	None
2 (Mild)	NF1 complications obvious, but these do not present a threat to the life of the individual	None
3 (Moderate)	Complications are a moderate threat to life, but can be managed with relative ease	May have a normal lifespan
4 (Severe)	Complications a serious threat to life, and difficult to treat	Shortened lifespan

Table 1. Classification of NF1 patients

Age	Sex	Severity	Site	Comorbidities/complications	Number of interventions	Outcome/Cosmesis
26	M	Grade 4	Right upper and lower extremities			
			Global	Scoliosis, Intrathoracic neurofibromas. Short stature. Dyspnea at rest.		
				Required tracheostomy for prolonged intubation	1	Died of pulmonary complications
16	F	Grade 2	Right orbitotemporal	None	2	Good
11	M	Grade 4	Left orbito-temporal	Pre-operatively left blind eye, non-functioning facial nerve.		
				Required tracheostomy for severe oral edema	2	Fair, but acceptable; has began school.
13	M	Grade 2	Left temporal	None	2	Good
18	M	Grade 1	Penis	None	1	Good
18	F	Grade 2	Left orbito-temporal	None	3	Fair
16	M	Grade 1	Chin	None	1	Good
21	F	Grade 4	Retroperitoneal	MPNST	1	Referred to oncologist
19	F	Grade 4	Upper and left lower limbs	MPNST	4	Referred to oncologist
12	M	Grade 3	Global Referred for debulking of			
			lower extremity and penile lesions	None	0	Under observation. No immediate indication for surgery
32	M	Grade 1	Middle finger			
			Global	None	1	Lost to follow-up
18	F	Grade 2	Scalp	None	2	Lost to follow-up
21	M	Grade 4	Left leg	MPNST	1	Good
17	F	Grade 2	Right orbito-temporal	None	2	Good
35	M	Grade 4	Retroperitoneal	MPNST	1	Referred to oncologist
10	F	Grade 2	Back	Leg plexiform neurofibromas	1	Good

Table 2. NF1 patient characteristics

this region (10-13). Neurofibromas constituted 12.5% of 225 primary neural tumors of the head and neck region, over a 10 year period in a Nairobi hospital, Kenya (14). Akadiri and Jackson aptly outlined the difficulties of surgical management in resource-poor environments (12).

The complications of NF1 may affect any system and are difficult to predict, even within families (1,15). Consequently the prognosis is uncertain for virtually all patients with NF1-related complications (1,16). NF1 is a progressive disorder; age is the most important determinant of NF1 severity, with a 25% estimated likelihood of developing grade 4 by age 30 years (Table 1) (3). The six patients (40%) with grade 4 lesions had an average age of 17.8 years. Patients with grade 1 and 2 lesions also had an average age of 17 years. The numbers in this study are small, and therefore difficult to draw any conclusions from, but the data does suggest that sub-Saha-

ran African NF1 patients may present with advanced lesions at an earlier age than in Western populations.

Fortunately, most NF1 patients never develop major complications (Table 2). The mainstay of their care is therefore anticipatory guidance and surveillance for treatable complications (1).

The three case presentations illustrate the difficulties associated with the surgical care of NF1 patients in sub-Saharan Africa. The availability of an intensive care unit was central to the care of two of the three patients presented. All three patients required blood transfusion for intra-operative hypotension from blood loss. One patient died peri-operatively from pulmonary failure. Although this possible outcome had been discussed, the potential anticipated gains from the surgery, especially mobility, independence and social interaction, outweighed the risks of the debulking operation.

Vascular and Cardiothoracic complications

Intrathoracic tumors can produce dyspnea, hemothorax and other serious complications (17). Vascular anomalies include aneurysms. Hypertension in NF1 patients may be secondary to a number of surgically correctable conditions, including: increased incidence of coarctation of the aorta, phaeochromocytoma and renal artery stenosis (which may be from aneurysm formation or extrinsic compression by an adjacent tumor) (3).

Abnormal vessels account for massive bleeding encountered during surgical debulking of neurofibromas, for which different techniques, including hypotensive anesthesia have been used (17). Peri-operative transfusion was necessary in eight (53%) of the 15 patients who underwent surgery. The diffuse but significant bleeding encountered in these patients is difficult to control even with cautery. Application of pressure dressings and undersawing with multiple deep sutures aid in the control of bleeding.

Skeletal complications

Skeletal involvement may include macrocephaly, dysplasia of the greater wing of sphenoid, bony defects of the skull, vertebral dysplasia, scoliosis, pseudoarthrosis (usually distal tibia and fibula) and a short stature amongst others (4,5). Non-ossifying cyst-like fibromas of the long bones, genu varum and genu valgum, cortical bone defects and focal bone gigantism can occur with variable frequencies. Pressure on bone from adjacent plexiform neurofibromas may lead to erosion or bone demineralization (18-21).

Central nervous system (CNS) and the spinal cord

A large head in patients with NF1 is usually due to macrocephaly. A child with NF1 and macrocephaly does not need to be investigated unless there are other symptoms or signs suggestive of intracranial pathology (1). About 50% of patients with NF1 have learning disabilities, some behavioral problems and a heightened risk of epilepsy and headaches. These seizures may be due to the existence of a recognized complication of NF1, such as tumors, hydrocephalus or cerebrovascular disease, but may be idiopathic or a consequence of non-NF1-related pathology (1).

Gliomas are well-recognized complications of NF1 (22). They most commonly involve the optic pathways, especially in children. Bilateral optic gliomas are considered by some as pathognomonic of NF1. Medulloblastomas and ependymomas have also been reported. The majority of NF1-associated CNS lesions may not require specific treatment (1). However, approximately 50% of patients may show clinical or radiological progression at some stage, with some experiencing symptoms or neurological deficits. Shehu and Hassan reported a case of an arachnoid cyst in a NF1 patient who had presented with quadriparesis, but recovered after surgery (23).

Other CNS complications include: migraine headaches, aqueductal stenosis, cerebrovascular disease, and spinal meningoceles, amongst others. An increased incidence of multiple sclerosis has also been reported (1).

Intraspinal and intramedullary tumors and spinal root neurofibromas usually present with impairment of pain and temperature sensation, reflex loss at the level of the tumor, sphincter disturbances or progressive paraparesis and generally have a poor outcome. Extraspinal plexiform neurofibromas may extend into the spinal cord leading to spinal cord compression and/or radiculopathies (15).

Neurofibromatosis neuropathy is a progressive sensorimotor peripheral neuropathy due to accumulation of multiple peripheral neurofibromata on the nerve roots. Hypotonia and poor muscle coordination affect some NF1 patients.

Plexiform neurofibromas

Features	Surgical complications	Incidence
Chest	Chest wall deformities	50%
	Fibrosing alveolitis	20%
Vascular	Vascular abnormalities	50%
	Hypertension	20% by age 60 yrs; (60% in pheaochromocytoma)
	Phaeochromocytoma	0.1 - 5.7%
	Renal artery stenosis (coarctation of abdominal aorta in 25%)	1-2%
Skeletal (25 - 40%)	Short stature	20-30%
	Pseudoarthrosis	2%
	Long bone dysplasia	3-4%
	Kyphoscoliosis	12-20%
	Spinal 'hour-glass' tumors	
	Pathological fractures	
	Sphenoid wing dysplasia	11%
	Skull defects	
	Macrocephaly	50%
Tumors/Malignancies	Neurofibromas (plexiform)	30%
	MPNST	1.0 to 1.6 per 1000 population
	Endocrine tumors	
	Breast cancer, Leukemia, Melanoma	
Gastro intestinal	Stromal tumors	7%
	Hemorrhage	
	Duodenal carcinoma	
Central nervous system	Optic gliomas	15-20%
	Aqueductal stenosis	1%

Table 3. Surgical complications of NF1

Plexiform neurofibromas are the second most common NF1 complication, after learning difficulties, affecting 30% of the NF1 patient population. They are clinically and pathologically a distinct entity from other types of neurofibromas. Plexiform neurofibromas are congenital lesions that present as large subcutaneous swellings, soft in consistency, with ill-defined margins. These lesions affect long portions of peripheral nerves and surrounding tissue, and often lead to significant disfigurement and mechanical pressure. Nowhere else do neurofibromas cause as much deformity however, as in the orbito-temporo-facial region. Here, the smallest neurofibroma produces a prominent abnormality, while larger ones can produce monstrous and even hideous deformities in a person (3,5,6,24-26) (Figure 3). Lesions in this region should therefore be resected/debulked in order to improve cosmesis and self/social acceptance, as in the second case presentation. Seven (44%) of the series of 16 patients presented with lesions of the head region, including four orbito-temporal plexiform neurofibromas. Plexiform neurofibromas are difficult to resect because of their diffuse nature, and the currently recommended protocol is conservative unless sudden enlargement of the mass, functional deficits, pain or bleeding from the mass develop (1).

Gastrointestinal complications

The commonest GI lesions are stromal tumors, located mostly in the stomach and jejunum. These may present with bleeding, obstruction, or perforation. Carcinoid tumors (usually duodenal or periampullary) are fairly

common GI lesions in NF1 patients (3,27,28).

Obstetrics

Authors have reported a higher incidence of preterm labor, Caesarian section rate, intra-uterine growth retardation and stillbirths amongst NF1 patients than in the general population. Most of these complications are related to hypertensive complications (29,30).

Malignant disease

Malignant tumors occur four times more frequent in the NF1 patient group than in the general population matched for age, gender, and time of follow-up (1). NF1 has a well established relationship with malignancies such as MPNST, CNS tumors, rhabdomyosarcomas, leukemia, and pheochromocytomas (7,22). Breast cancer, Non-Hodgkin's lymphomas and Wilm's tumors amongst others have also been reported in patients with NF1 (22). MPNSTs may also arise as second tumors in the field of irradiation for another neoplasm. Triton tumors occur at a younger age and have a poor prognosis (31).

MPNSTs, the commonest malignancies in NF1 patients, can occur at any site in the peripheral nervous system, most commonly from plexiform neurofibromas. They represent 10% of all soft tissue sarcomas; 50% of all MPNSTs occur in NF1 patients. Twenty five percent of the patients in the current study had MPNSTs; two of the 4 patients had radiological evidence of metastases.

Surgical management

Total excision of localized neurofibromatosis with skeletal and soft tissue reconstruction has had favorable long term results, but is rarely achievable. Excision requires multiple stages in the most extensive lesions (31-35). The extent of resection has proven prognostic significance in children; a greater extent of surgical resection predicts both lower risk of tumor progression and longer interval to progression. Near-total or sub-total excision of the tumor ensures recurrence rates less than 20% and 40% respectively, while removal of less than 90% of the tumor mass leads to a recurrence rate of 60% or greater (37-40).

Total resection and reconstruction is, however often tempered by the inability to perform total excisions of lesions in the head and neck, because of the need to preserve vital structures, such as the seeing eye, or the functional facial nerve (3,40). Functioning upper and lower extremity nerve plexuses are deterrents to total resection in the limbs. Plexiform neurofibromas involving the trunk and limbs may lead to soft tissue overgrowth, and even gigantism. The use of prosthetic mesh in the face has been shown to be effective in the long-term prevention of recurrence and drooping of tissue in the facial region; it acts as an inelastic subcutaneous fascia layer (39). Prosthetic mesh was used in the four patients with orbito-temporal neurofibromas in the current study.

Near-total excision was only possible in two patients: one who had a chin lesion and a second with a penile lesion. The other patients underwent what were largely debulking procedures due to the extensive nature of their lesions.

Timing of operation and extent of resection

Early resection may help minimize cosmetic and functional complications. However, recurrences are common in patients aged ten or less, after incomplete resection and in tumors located in the head and neck region.

The multiple procedures required in order to obtain acceptable cosmesis and reduce recurrences, are a significant strain on resources. In the experience of the authors, the primary determinants of the extent of resection in sub-Saharan Africa therefore include: finances, skilled manpower, availability of safe blood for transfusion, and access to an intensive care unit (for some patients). Therefore, only the single-stage procedure likely to obtain the best functional and cosmetic result, with the least risk to the life of the patient, should be performed. Emergency surgical intervention may be required in cases such as acute intestinal obstruction, acute hemorrhage into a lesion, acute neurological deterioration due to an enlarging lesion, or a life endangering mediastinal tumor (3, 41).

Peri-operative considerations

Prior to intubation and administration of anesthesia, cervical spine stability should be ensured. Kyphoscoliosis and fibrosing alveolitis, found in two percent and 20% of NF1 patients respectively, may increase the perioperative respiratory complications (42). Severe intraoperative bleeding is a feature reported by many, the result of abnormal vasculature including vascular stenoses, aneurysms, and arteriovenous fistulae (33,41-44). Blood for transfusion must be available before proceed-

ing with the surgery. The use of tourniquets on extremities significantly reduces blood loss during surgical excision (45). Other techniques used include pre-operative angiography and embolization, undersawing of the neurofibroma prior to excision as well as intra-operative wound packing with gauze.

Post-operative edema, that may occasionally make the initial surgical result appear worse than the pre-operative pathology is a troublesome complication that resolves over the course of a few weeks (44). Indeed in the oro-facial region, post-resection edema may necessitate a tracheostomy, to obviate the need for prolonged intubation, as in two of the three case reports in this study.

While malignancy (MPNSTs and other soft tissue sarcomas) is the leading cause of death in adults, intracranial tumors are the main cause of mortality in children. Acute hemorrhage (gastro-intestinal and intracranial), hypertension and its related complications are other important causes in adult deaths, with MPNSTs and leukemia being other causes of pediatric mortality (17).

Conclusions

Surgical symptom control (cosmesis, function, and pain) rather that surgical cure is the primary, achievable goal of most interventions in patients with NF1. Lifelong surveillance is necessary for all NF1 patients to avert or minimize complications.

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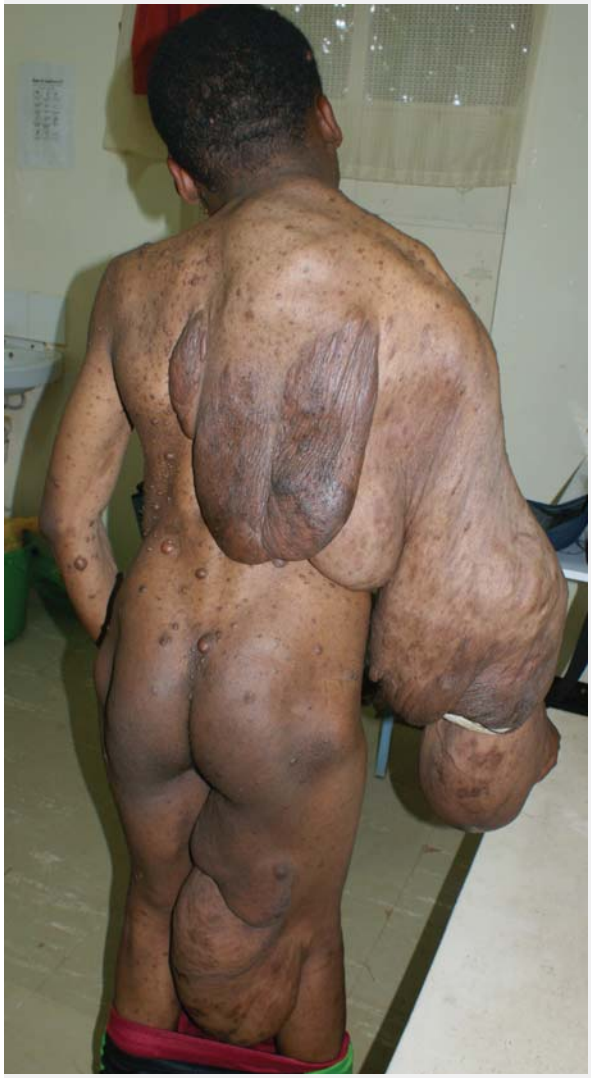

Figure 1
Patient with multiple, extensive plexiform neurofibromas, immobilized both by the weight of the lesions, as well by other lesions in the thoracic cavity.

Figure 2
Penile neurofibroma

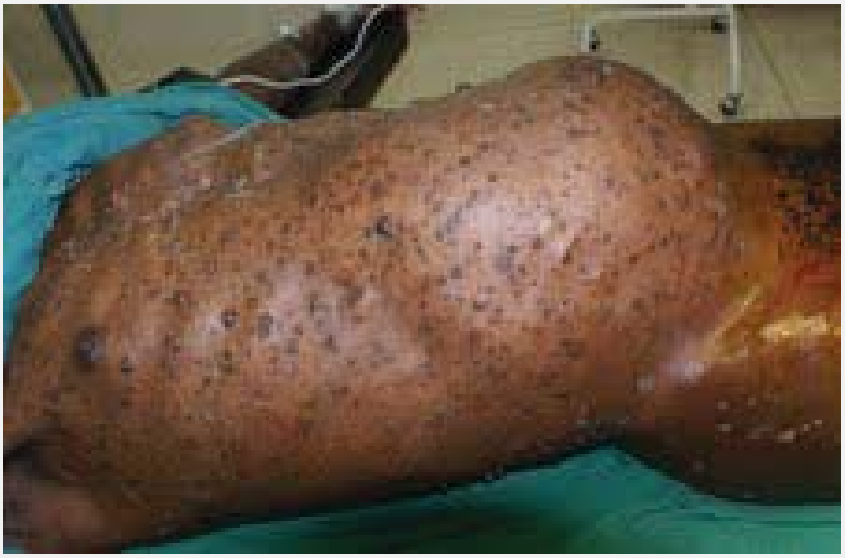

Figure 5
Retroperitoneal peripheral malignant nerve sheath tumor causing abdominal distension and obstruction.

Figure 3
Orbito-temporal plexiform neurofibroma, pre-operatively.

Figure 4
Same patient in figure 3, after two resections. Non-absorbable mesh was placed beneath the skin, to perform the function of a fascial layer, to help prevent sagging of facial skin, and hence recurrence.