MALIGNANT PERIPHERAL NERVE SHEATH TUMOURS IN ASSOCIATION WITH NEUROFIBROMATOSIS TYPE 1:

A case series and discussion of resources and pitfalls in management in the Western Cape

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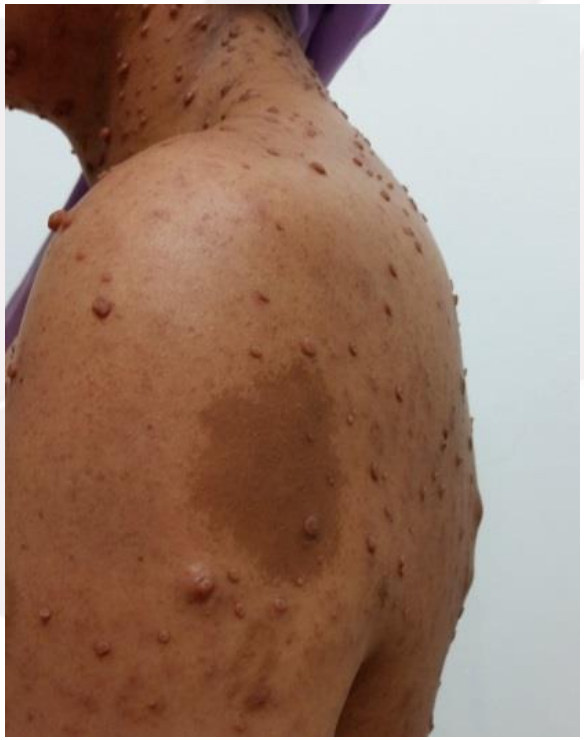
NF1: Introduction

- Relatively common **neuro-cutaneous** disorder affecting 1:3000 live births
- Autosomal dominant germline mutation in NF1 **tumour suppressor gene** (17q11.2)
  - 50% Familial: 50% De novo

NF1: Clinical manifestation

- **Skin**: Café-au-lait macules, skin-fold freckling
- **Skeletal**: Scoliosis, facial dysplasia, bowing of long bones
- Hypertension
- Cognitive and behavioral abnormalities
- **Benign tumours**: Gliomas (optic, central), neurofibromas, GIST, pheochromocytoma
- **Malignant tumours**: Peripheral Nerve Sheath Tumours (MPNST)



MPNST in NF1

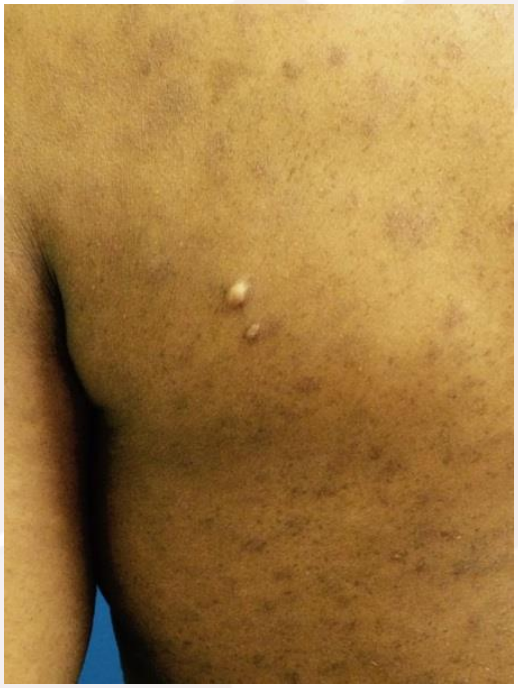
- MPNST
  - **Rare**, high grade, sarcoma of peripheral nerve elements
  - Sporadic or associated with NF1
  - Aggressive local invasion, poor prognosis
- MPNST in NF1
  - Lifetime risk **8-13%**
  - Younger age, advanced stage, multicentric
  - Prognosis inferior to sporadic MPNST
  - Leading cause of death in NF1
- **Suboptimal management**
  - Delayed referral and diagnosis
  - Management outside of Multidisciplinary team

Methods: Case series

- **We describe 4 cases of MPNST in patients with NF1 referred to the TBH Sarcoma Multidisciplinary Team (SMDT) during 2015 and 2016**
  - Retrospective review
  - Describe demographics, clinical features, stage, histology, treatment and survival outcomes
  - Identify pitfalls in diagnosis and management

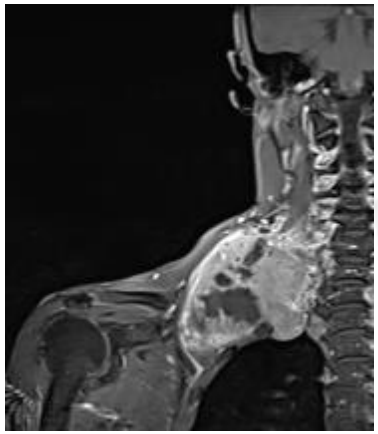
Case 1: Characteristics

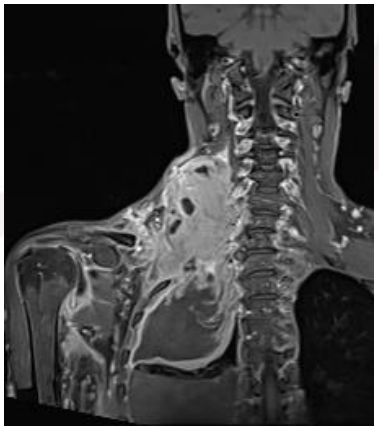
Characteristic	Case 1
Age	37
Gender	Male
First specialist contact	Neurosurgery
NF1 diagnosis	Pre-MPNST
Familial NF1	Yes
Primary site	Brachial plexus
AJCC Stage group (2010)	3 (T2bN0M0G3)

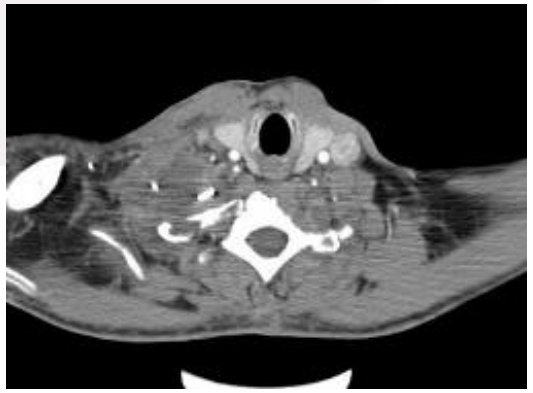


Case 1: Timeline

- **0** • 3yr history mass left shoulder
- **1** • MRI L brachial plexus: 11 x 8cm mass arising from cervical nerve roots
- **6** • **Excision:** HG MPNST, fragmented, 500g, margins positive
  • **No referral to SMDT**
- **8** • **PD:** Unresectable local recurrence
- **9-11** • **SMDT**
  • Pall **CRT**
- **12** • **PD** (lung mets)
- **13-16** • Pall **chemo** x 6
- **17** • **PD**
- **21** • Alive with PD







Case 2: Characteristics

Characteristic	Case 2
Age	36
Gender	Male
First specialist contact	Dermatology
NF1 diagnosis	Pre-MPNST
Familial NF1	Unknown
Primary site	Chest wall
AJCC Stage group (2010)	3 (T2aN1M0G3)

Case 2: Timeline

0
- 8m history mass chest wall
- **Biopsy:** Pleomorphic sarcoma

1
- **SMDT**
- Staging investigations & WLE

2
- CT chest: 6 x 8cm mass invading chest wall muscles, axillary node, no mets
- **WLE:** HG MPNST, close margins

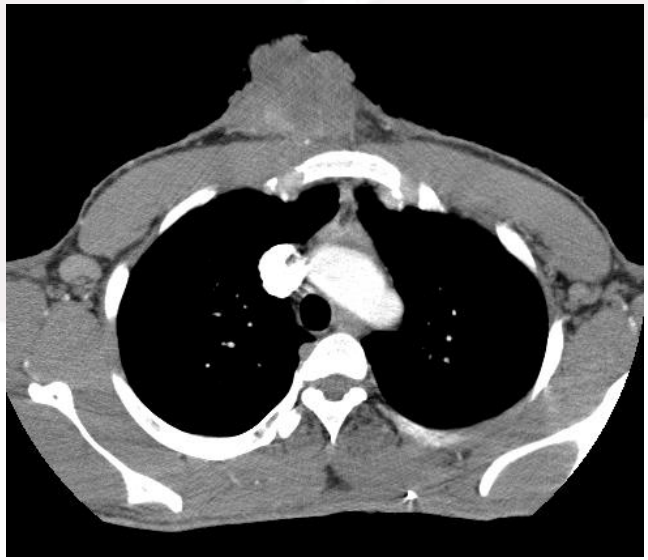
3
- **SMDT**
- FNA R Axilla node = Reactive
- RT primary

4
- **DNA RT**

5
- **SMDT**: Represented with **Nodal PD**
- Lymph node dissection

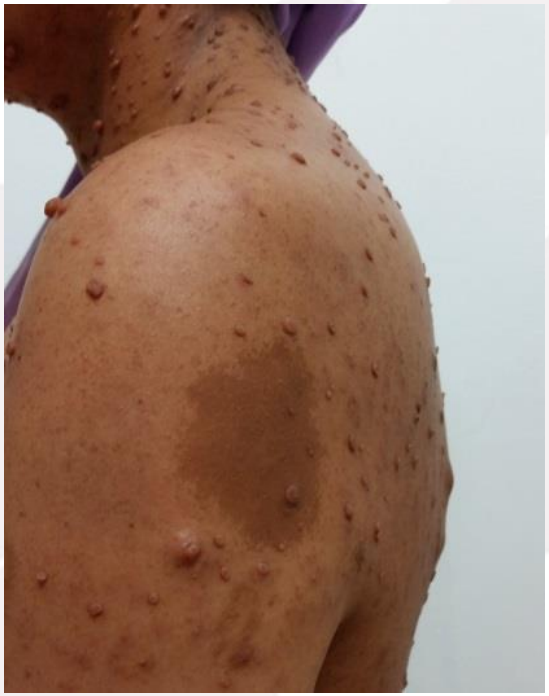
6
- **DNA LND**

7
- **Axillary lymph node dissection**
- Lost to FU



Case 3: Characteristics

Characteristic	Case 3
Age	38
Gender	Female
First specialist contact	General surgery
NF1 diagnosis	Pre-MPNST
Familial NF1	No
Primary site	Chest wall
AJCC Stage group (2010)	2B (T2bN0M0G2)



Case 3: Timeline

0
- 2yr history mass right chest wall since pregnancy
- **Biopsy:** MPNST

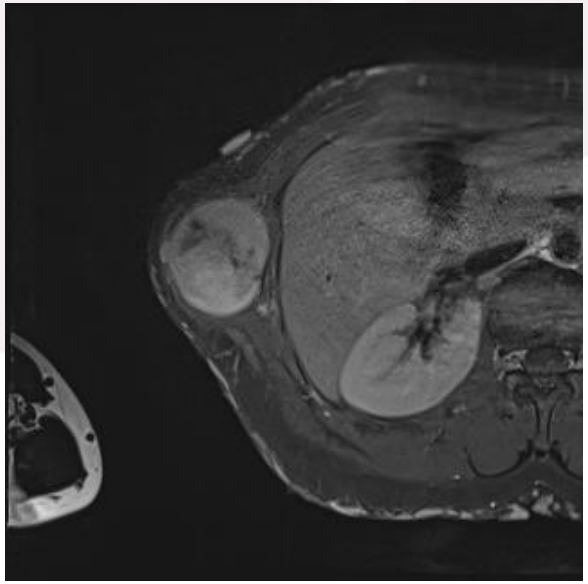
2
- MRI: 4 x 6 x 5cm mass arising from intercostal muscles, no rib erosion

3
- **WLE:** MPNST, close margins
- **SMDT**
- CT chest, Adjuvant RT & chemo

5-7
- **Adjuvant RT** 66GY

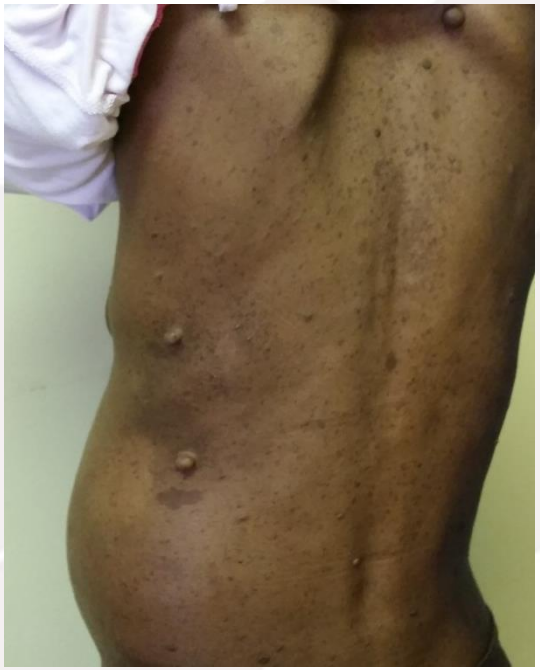
8-10
- **Adjuvant chemo**

10
- Alive with CR



Case 4: Characteristics

Characteristic	Case 4
Age	33
Gender	Female
First specialist contact	Urology
NF1 diagnosis	Post-MPNST
Familial NF1	Yes
Primary site	Retroperitoneum
AJCC Stage group (2010)	4 (T2bN0M1G3)



Case 4: Timeline

0
- 5m history mass left flank, since pregnancy
- Abdominal CT = MPNST

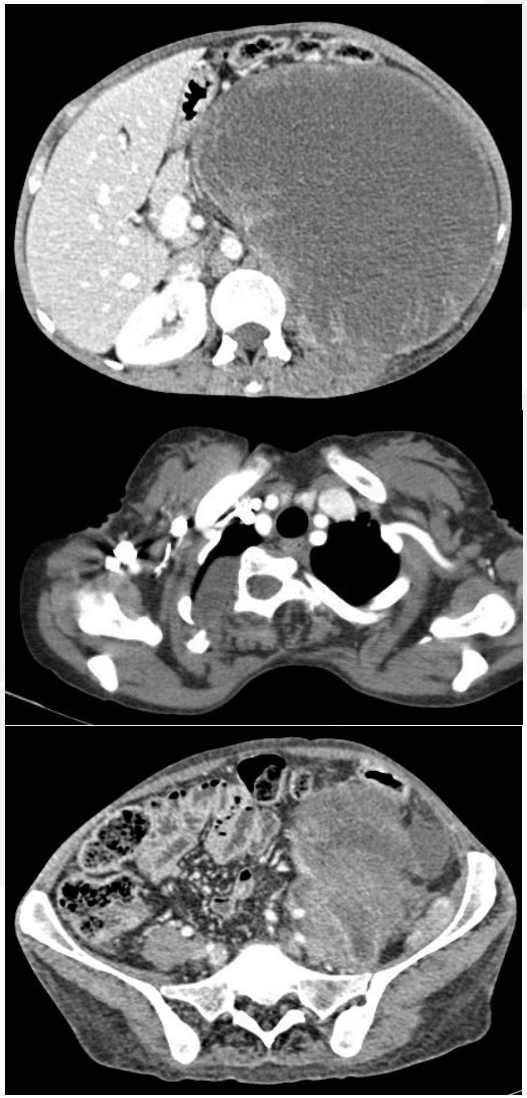
1
- **Biopsy:** Spindle cell tumour, NOS
- Chest CT: Lung met, pleural effusions

2
- **Biopsy:** HG Sarcoma
- Abdo CT: **PD** (intra-abdominal mets)

3
- **SMDT**
- Palliative **chemo** x 6

5
- Restaging Abdo CT: **SD**

6
- Alive with stable metastatic disease



NF1: Wide variability in clinical presentation

- 97% develop features by age 8yrs
- Cutaneous and subcutaneous neurofibromas
  - Visible from about 4yrs with hormone associated flares
  - Low potential for malignant transformation
- Deep plexiform neurofibromas
  - Present at birth and enlarge during the first decade
  - Higher potential for malignant transformation
- 20% develop serious complications and mostly during childhood

NF1: Diagnostic criteria

- A clinical diagnosis is based on the presence of 2 or more diagnostic criteria for neurofibromatosis 1 developed by the National Institutes of Health (NIH, 1988)
  - Six or more **café-au-lait macules** over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals
  - Two or more **neurofibromas** of any type or one plexiform neurofibroma
  - **Freckling** in the axillary or inguinal regions
  - **Optic glioma**
  - Two or more **Lisch nodules** (iris hamartomas)
  - A distinctive **osseous lesion** such as sphenoid dysplasia or tibial pseudarthrosis
  - A **first degree relative** (parent, sib, or offspring) with NF1 as defined by the above criteria

NF1: Diagnostic criteria

- Internationally, **clinical diagnosis** predominates
  - Large NF1 gene complicates molecular testing and increases **cost**
- Genetic molecular testing reserved
  - Prenatal testing
  - Difficult clinical diagnosis
- Diagnosis made by wide variety of specialist
  - **Paediatricians**, Neurologists, child psychiatrist, dermatologists, obstetricians, surgeons, oncologists

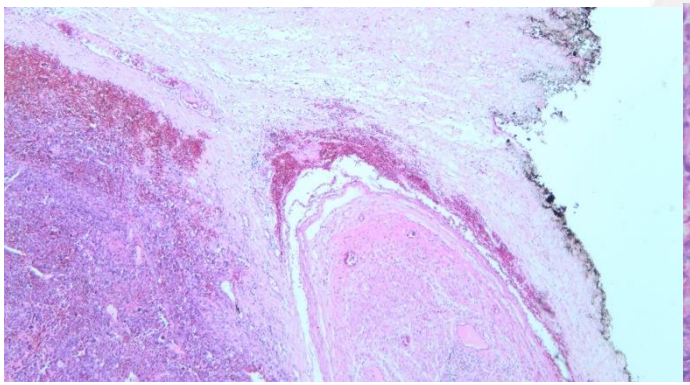
MPNST in NF1: Clinical presentation

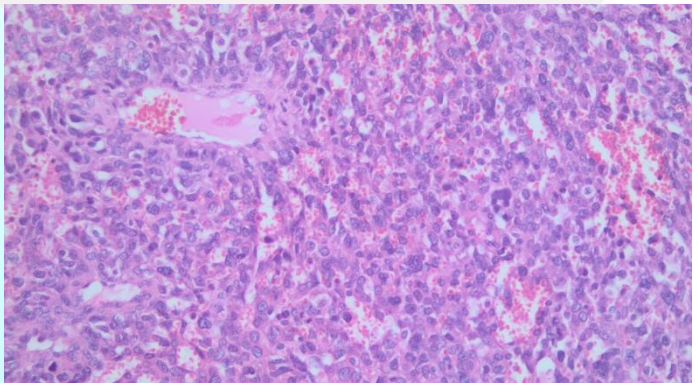
- MPNST most often arise in deep plexiform neurofibromas
- No gender predilection
- Median age 20-40yrs
- Firm, painless, enlarging mass, neuropathic symptoms
- Malignant transformation during pregnancy reported
- Differential diagnosis: Other soft tissue sarcomas, lymphoma

MPNST: Histological diagnosis

- MPNST is a malignancy
  i. from a peripheral nerve
  ii. from a pre-existing benign peripheral nerve sheath tumour
  iii. in patients with NF1

- Outside the above scenarios extensive immuno-histochemical and molecular testing is required for diagnosis because of the diverse morphology
- Heterologous elements such as bone, cartilage, skeletal muscle, smooth muscle and angiosarcomatous differentiation seen





MPNST: Staging investigations

- AJCC TNM staging system (10th ed, 2010)
- MRI
  - Anatomical extent of the lesions
  - Planning surgery and/or radiotherapy
- Chest CT
  - High risk of pulmonary metastases
- FDG-PET not standard of care

MPNST: Management

- Follows guidelines for adult soft tissue sarcomas and relies heavily on a **multidisciplinary approach**
- Mainstay of curative treatment is **surgery**
  - Complete excision with wide margins
- **Radiotherapy** & **Chemotherapy**
  - RT before or after surgery allows conservative surgery
  - Reduces recurrence risk in **high risk tumours**
    - Size >5cm
    - Close resection margins (<1cm)
    - Grade 2-3 tumours
    - Deep seated lesions

MPNST in NF1: Outcomes are improving

- 5yr OS vs sporadic MPNST
  - 1986: **16%** vs 53%
  - 2009: 35% vs 60%
  - 2013: **45-54%** vs 46-75%

- **Meta-Analysis** 2013 (N >1800, 48 studies)
  - OR for death from NF1-MPNST pre vs post 2001
  - 1.68 vs 1.47 (p=<0.05, 95% CI >1)

- Poor prognostic factors
  - **Size**
  - No proven biological difference

Series: Outcomes

- From **presentation** to TBH

Parameter	Case 1	Case 2	Case 3	Case 4
Treatment	2m	6m	3m	3m
PD	5m	8m	NA	2m
OS	7m (Alive with PD)	21m (Alive with mPD)	10m (Alive with CR)	6m (Alive with mSD)

Current pitfalls in management

- The exact **prevalence** of NF1 in South Africa is not well documented
- Patients are often diagnosed and monitored in childhood, but close follow-up does not continue into **adulthood** when the risk of serious complications like MPNST is at its highest
- There is currently no surveillance program for NF1 adults (>18yrs) in the Western Cape public health system
- Inadequate **patient education** and insight
- **Non-centralized** NF1 care leads to delays in diagnosis and treatment
- **Multidisciplinary** management not standard

MPNST: Delays in management

- 3 cases presented with locally advanced or metastatic disease
- 3 cases had large, superficial lesions

- **Patient** factors
  - Lack of knowledge and insight
  - Fear of stigmatization
  - Lack of access to health care
- **Service** delays
  - Known delays in appointments, imaging, surgery and histology review
  - Average 3.5m (2-6m) delay from presentation to TBH to start of treatment

- **Unacceptable** in the management of an aggressive malignancy

Suggested surveillance strategy for adults (>18yrs) with NF1

- Annual physical examination by **general practitioner**
  - Skin and Neuro-skeletal exam
  - Blood Pressure assessment
  - Special investigations as indicated by clinical signs or symptoms
- Monitoring of established NF1 complications by an appropriate **specialist**
- High index of suspicion and **early referral for MPNST**
- Patient **education** on inheritance of NF1, pregnancy related complications and avoidance of radiotherapy
- Psycho-social and occupational **support** for self-esteem and cognitive problems

Patient driven surveillance

- **Empower** and support patients to manage their own health care
  - Medical Genetics **Leaflet**

- Establish **centralized NF clinics** in academic hospitals
  - Multidisciplinary collaboration well established
  - Consensus diagnosis of difficult cases
  - Contact point for rapid referral and expedited diagnosis and management of complications of NF
  - Education of patients and health care professionals
  - Research

Conclusion

- MPNST is a rare, but aggressive malignancy with poor survival outcomes, particularly in patients with NF1
- Early diagnosis and appropriate treatment of MPNST can possibly prevent the poor outcomes and extensive treatment required in the current series
- We propose the establishment of centralized adult NF1 clinics in academic hospitals that can oversee and manage a patient driven health surveillance program

References available on request

Dankie
Thank you
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