Malignant transformation of Neurofibromatosis

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5 year old boy, recently adopted from eastern Europe

Parents worried about his facial asymmetry and the “swelling” of his right shoulder and neck since birth

Otherwise “normal 5 year old”

No pain
History:

- Recently adopted from an orphanage in eastern Europe, little is known about biologic mother and father

- No past medical/surgical history
Our patient: Physical examination

- Physical examination:
  - well-appearing child, alert and cooperative
  - **Increased soft tissue** of doughy consistency on right side of face, neck and shoulder
  - Multiple skin lesions:
    - Brown freckles in his axillae
    - Large macular hyperpigmentation (25 x 30 cm) on shoulder
    - > 20 brown macules > 0.5 cm in diameter on whole body
  - No other abnormalities found in the remainder of the physical examination and in a detailed neurologic examination
Our patient:  Soft tissue tumor

Our patient has unilateral increased soft tissue, id est in other words:

→ a soft tissue tumor.

What are the differential diagnoses for soft tissue tumors?
Our patient: Differential diagnosis

**WHO classification of soft tissue tumours**

**ADIPOCYTIC TUMOURS**
- Benign: Lipoma, Liposarcoma, Lipomatosis of nerve
- Malignant: Liposarcoma, Lipoblastomatosis

**SKELETAL MUSCLE TUMOURS**
- Benign: Rhabdomyoma, adult type, fetal type, genital type
- Malignant: Embryonal rhabdomyosarcoma (incl. spindle cell, botryoid, anaplastic)

**INTERMEDIATE (locally aggressive)**
- Lipoblastomatosis

**VASCULAR TUMOURS**
- Benign: Haemangiomas of subcutaneous tissue: capillary, cavernous, arteriovenous, venous

**SO-CALLED FIBROHISTOCYTIC TUMOURS**
- Benign: Giant cell tumour of tendon sheath, Diffuse-type giant cell tumour

**FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS**
- Malignant: Primary fibrosarcoma

**TUMOURS OF UNCERTAIN DIFFERENTIATION**
- Benign: Infraspinatus myxoma
- Malignant: Mixed tumour, Myxofibrosarcoma, Synovial sarcoma


→ Detailed investigation with imaging needed!
Having these WHO differential diagnoses in mind, the workup of our patient included

X-Ray,  
Ultrasound, and  
MRI,

for further evaluation of his soft tissue tumor.
Findings:
Increased soft tissue of the patient’s face, neck and shoulder on the right side (ellipse). Also compare difference of cheek size right and left (arrows).
Our patient: Expansive soft tissue tumor

Findings:
Expansive soft tissue tumor (around blue line) with unilateral skin folding (▷), pushing the trachea (Δ) to the left lateral of spinous processes (+).

In addition, extra density (*) projecting at the apex of right lung and a soft tissue skin nodule (↑) on shoulder.
Our patient: Nerve sheath tumor

Findings:
Sonogram shows a well-defined and hypoechoic mass (#) with posterior acoustic enhancement (+). Note direct continuity with a nerve (*).
Findings:

Extensive, infiltrative lesion of the skin (※) and subcutaneous tissue of the anterior chest wall, that extends into the apex of the right hemithorax and surrounds the brachial plexus. Lesion and infiltration are roughly marked by the yellow circle.
Findings:
Extensive, plaque-like lesion of the skin (★) and subcutaneous tissue that extends into neck (▲) and shoulder (+), surrounds the brachial plexus (not shown) and extends into the apex of the right hemithorax (x).

Lesion and area of infiltration are roughly marked by yellow lines.

Impression:
Axial and coronal MRI show a plexiform neurofibroma
Our patient: Diagnosis Neurofibromatosis type 1

Summary of our patient’s findings:

- > 20 cafe-au-lait macules
- Axillary freckling
- Plexiform neurofibroma

→ Enough criteria for Neurofibromatosis type 1, because...


Companion patients with cafe-au-lait macules (A) and axillary freckling (B)
Diagnostic criteria Neurofibromatosis Type 1 (NF1)

...according to the National Institutes of Health (NIH) the patient should have 2 or more of the following diagnostic criteria for the diagnosis Neurofibromatosis type 1:

- 6 or more café-au-lait spots
- ≥ 2 neurofibromas of any type or ≥ 1 plexiform neurofibroma
- Freckling in the axillae or groin
- Optic glioma
- ≥ 2 Lisch nodules
- Dysplasia of the sphenoid; dysplasia or thinning of long bone cortex
- First degree relative with NF1.

Our patient has the three findings **typed in blue** and therefore was diagnosed Neurofibromatosis type 1.
What is Neurofibromatosis Type 1 (NF1)?

- First described in 1882 by Friedrich von Recklinghausen
- Worldwide incidence 1 : 3500
- Autosomal-dominant disorder
- Responsible gene isolated in 1990
- Loss-of-function of the tumor suppressor gene NF1

Friedrich von Recklinghausen

The gene NF1 encodes the protein Neurofibromin (NF-1), which regulates the Ras-pathway involved in cell division of nerve sheaths (a in figure above).

Loss of function of NF-1 causes an unregulation of the pathway. This leads to pathological neurite elongations (b in figure above) and the development of neurofibromas.

Neurofibromas are the main characteristic for Neurofibromatosis Type 1.
Characteristics of NF1: Nodular neurofibromas

3 clinically and histologically different types of Neurofibromas:

- 95% of patients: discrete nodular neurofibromas (skin and peripheral nerves at any site, benign)
Companion patient 1: Nodular neurofibromas

Pictures of a patient with severe neurofibromas of the skin

Characteristics of NF1: Plexiform neurofibroma

3 clinically and histologically different types of Neurofibromas:

- 95% of patients: discrete nodular neurofibromas (skin and peripheral nerves at any site, benign)
- 30% of patients: plexiform neurofibromas (affect long portions of nerves, 2 - 16% turn malignant)
Characteristics of NF1: Optic nerve glioma

3 clinically and histologically different types of Neurofibromas:

- 95% of patients: discrete nodular neurofibromas
  (skin and peripheral nerves at any site, benign)

- 30% of patients: plexiform neurofibromas
  (affect long portions of nerves, 2 - 16% turn malignant)

- 15% of patients: optic nerve gliomas
  (malignant, very slow growing, sometimes self-limiting)
Companion patient 2: Optic nerve glioma

MRI brain, T1 weighted, without contrast, two different axial slides

Findings: Bilateral enlargement of the optic nerve, right (→) bigger than left (→), with infiltration of the optic chiasm (→). As seen, optic gliomas are typically hypointens ("darker") compared to orbital fat (★), isointense to the cortex (+) and hypointens to the white matter (x) on T1 weighted MRI images.
Neurofibromatosis Types 1 and 2

Talking about one type of Neurofibromatosis, the second type should also always be mentioned for completion. This is in our case:

Neurofibromatosis type 2.
What is Neurofibromatosis Type 2 (NF2)?

- Autosomal dominant disorder
- Prevalence 1: 210,000
- Loss-of-function of tumor suppressor gene NF2
- Main manifestation:
  Bilateral schwannomas of vestibular branch of cranial nerve VIII.

**Findings:**
Bilateral contrast enhancing olive shaped tumors (▲) adjacent to the internal auditory meatus (yellow arrow →).

Axial MRI head, T1 weighted, with contrast

Image courtesy Mai-Lan Ho, MD
Treatment of Neurofibromatosis 1 and 2

- Genetic disorders → no causal therapy
- Watchful waiting and monitoring
- Surgery, if neurofibroma / schwannoma
  - grows rapidly or changes in consistency,
  - causes problems (neurologic, cosmetic etc.) or is painful.

So what happened to our patient?
Our patient: Medical treatment

- Closely monitored with yearly MRI and detailed physical examination

- Plexiform neurofibroma remained stable with no symptoms for 4 years

Then:
- Pain in right shoulder
- Neurofibroma with increased mass at the area of apex of the right lung seen on MRI compared to older images

→ Further evaluation with PET-CT
Our patient: New mass with avid uptake

Findings:
Normal isotope uptake in tonsils, thymus, heart, renal collection systems and bladder (arrows, marked from above). Area of avid, pathological uptake in right shoulder (red circle). This area is seen as defined mass with high activity on the integrated PET-CT. Malignancy possible.
Our patient:  Further treatment

Biopsy of the mass seen on PET-CT to verify its dignity:

**Histopathology:** Atypical neurofibroma or low grade malignant nerve sheath tumor.

→ Surgical resection (incomplete due to size)

NOW: Treatment with PEG-interferon alpha-2B (Phase II study, National Cancer Institute)
Complete surgical removal of our patient’s malignant tumor is not possible due to its size and location. Also there are no known medical treatments for Neurofibromatosis so far.

For this reason, the national study with PEG-Interferon alpha-2B is the only available therapy option for our patient at this point. And the study will show (completion in 2012), if this drug can be used for a successful treatment of malignant transformations of neurofibromatosis.
References

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