Educational Case: Peripheral Nerve Sheath Tumors

Matthew C. Welch, BS¹, and Alison R. Huppmann, MD¹

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, peripheral nervous system, neurofibroma, schwannoma, malignant peripheral nerve sheath tumor, neurofibromatosis

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Primary Objective
NSP2.2: Tumors of the Peripheral Nervous System. Compare and contrast the common benign from malignant PNS tumors and outline their molecular basis and clinicopathologic features.

Competency 2: Organ System Pathology; Topic NSP: Nervous System: Peripheral Nervous System and Eye; Learning Goal 2: PNS Neoplasia.

Secondary Objective
NSP1.3: Neurofibromatosis. Compare and contrast the clinicopathologic features of neurofibromatosis types 1 and 2.

Competency 2: Organ System Pathology; Topic NSP: Nervous System: Peripheral Nervous System and Eye; Learning Goal 1: Peripheral Nerve Disorders.

Patient Presentation
A 6-year-old girl presents to her pediatrician due to a “lumpy place” in her neck. The solitary lesion is not tender and was first noticed at least a few months ago. It has gradually been getting larger. She has no significant past medical history, and her family history identifies only hypertension in her paternal grandfather. Physical examination reveals a 4-cm firm, lobulated mass on the right side of the neck.

Diagnostic Findings, Part 1
Magnetic resonance imaging (Figure 1) shows a hyperintense subcutaneous mass in dermal and subcutaneous tissue. A resection is performed, with the gross and representative histologic findings illustrated in Figures 2 and 3.

Questions/Discussion Points, Part 1
Describe the Gross and Histologic Features in Figures 2 and 3. What Is the Most Likely Diagnosis?

Figure 2 demonstrates a tan-white multilobulated mass in the dermis and subcutaneous tissue. The low-power microscopic image in Figure 3A reflects these findings, with a mass seemingly composed of many separate nodules that are present in the mid-dermis and extend into subcutaneous adipose tissue.

¹ Department of Pathology, School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, USA

Corresponding Author:
Alison R. Huppmann, Department of Pathology, School of Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Rd, Bethesda, MD 20814, USA.

Email: alison.huppmann@usuhs.edu
An intermediate power image of one of the nodules seen in Figure 3B shows eosinophilic bundles of collagen. Interspersed nuclei can be seen; the lesion is not highly cellular. High power (Figure 3C) shows that the nuclei are elongated and wavy. Mitotic figures are not identified.

The histological and clinical features of this mass are suggestive of a plexiform neurofibroma. Of the different forms of neurofibroma, a benign tumor, the plexiform type produces a ropy or tortuous appearance grossly or at low power, sometimes referred to as a “bag of worms.” This appearance is due to tumor growing within multiple adjacent, enlarged fascicles of peripheral nerve. Each fascicle appears well delineated since the surrounding perineurium is preserved.\(^1\) Plexiform neurofibromas are found exclusively in patients with the genetic disorder neurofibromatosis type 1 (NF1) and are the only form to have a high risk of malignant transformation.\(^1,2\) The location and size of the tumor determine clinical presentation.

**What Are the Other 2 Major Types of Neurofibromas (Based on Growth Pattern)? Describe the Clinicopathologic Features of Each**

While all neurofibromas are derived from a neoplastic proliferation of Schwann cells, they can be classified based on growth patterns through local tissue (as opposed to individual cellular morphology or genetic markers). The 2 other major types of neurofibroma include superficial cutaneous (also called localized) and diffuse types. Superficial cutaneous neurofibromas are frequently solitary (unless associated with a genetic disorder) and do not transform into malignant tumors; their growth is often intraneural\(^3\) and their removal is usually reserved for cosmetic reasons.\(^2\) Diffuse neurofibromas clinically present as thickened plaques as they grow in the dermis and subcutaneous area, often involving surrounding tissue such as fat and cutaneous appendages as they spread (Figure 4A).\(^1\)

Histologically, all neurofibromas contain a disorganized mix of cellular components, including not only the neoplastic Schwann cells but also other non-neoplastic cells such as fibroblasts, CD34\(^+\) spindle cells, and perineurial-like cells. The cells are admixed with collagenous to mucinous matrix. Mast cells are often intermixed (Figure 4B).\(^1\) Cellularity within the mass varies,\(^3\) but the neoplastic Schwann cells grow in a wavy and interlaced pattern and show hyperchromatic, spindle-shaped nuclei.\(^2\) In addition to the clinical appearance, differentiation of diffuse from localized tumors may be possible based on involvement of surrounding tissue as seen on low power and the presence of pseudo-Meissner corpuscles (also known as tactile-like bodies; Figure 4C).

**Diagnostic Findings, Part 2**

Following a detailed physical examination, 7 flat, pigmented macules/patches are identified on the skin (Figure 5), and freckles are present in the axillae.

**Questions/Discussion Points, Part 2**

**What Is The Significance of the Additional Physical Exam Findings in This Patient?**

Solitary cutaneous neurofibromas are not particularly concerning given that most neurofibromas are sporadic. The identification of a plexiform neurofibroma suggests that the patient has NF1, but specific diagnostic criteria must be met to render this diagnosis (see Table 1).\(^4\) Café au lait macules (≥6) and axillary freckling in the setting of a plexiform neurofibroma confirm the diagnosis of NF1 in this patient.

**Discuss the Genetics of Neurofibromatosis Type 1**

Also referred to as von Recklinghausen disease, NF1 is a relatively common autosomal dominant genetic disorder (incidence of 1 in 3000 persons) caused by alterations in the NF1 gene on chromosome 17.\(^4\) Loss-of-function mutations can be due to either a pathogenic version of the gene (over a
thousand have been identified) or a deletion, both resulting in a deficiency of the gene product, a tumor suppressor protein called neurofibromin. Neurofibromin inhibits the activity of RAS by stimulating a GTPase (RAS must be bound to GTP to be active). Tumors that may occur in these patients include all types of neurofibromas, malignant peripheral nerve sheath tumors, and plexiform neurofibromas. Figure 3 shows the histological characteristics of neurofibromas.

**Figure 3.** A, Histologically, multiple well-defined tumor nodules are present in the dermis and subcutaneous adipose tissue (hematoxylin and eosin, ×1). B, Higher power of one of the nodules shows scattered basophilic nuclei within a collagenous background (hematoxylin and eosin, ×100). C, The wavy, bland-appearing nuclei belong to the tumor cells (hematoxylin and eosin, ×400).

**Figure 4.** A, Scanning magnification of this diffuse neurofibroma shows extensive involvement of the dermis with extension into subcutaneous adipose tissue (arrow). The arrowhead indicates some of the eccrine glands surrounded by the tumor (hematoxylin and eosin, ×1). B, The mixture of different cell types admixed with the neoplastic Schwann cells is visible in this higher power, as nuclei of different shapes and sizes are seen. Mast cells (circle) are usually identified within neurofibromas (hematoxylin and eosin, ×400). C, Diffuse neurofibromas may also contain structures resembling Meissner corpuscles (hematoxylin and eosin, ×400).

**Figure 5.** This lightly pigmented macule measures approximately 8 mm. This patient had multiple similar-appearing lesions on other parts of the body ranging from 6 mm to 2.1 cm that were not photographed. These are consistent with café au lait macules.

**Table 1.** Diagnostic Criteria for Neurofibromatosis Type 1 (NF1).

| Criterion | Morphological Features |
|-----------|------------------------|
| cafés au lait macules (>5 mm for prepubertal persons, >15 mm for postpubertal persons) | 6 or more café au lait macules (>5 mm in greatest dimension) |
| Axillary or inguinal freckles | 2 or more freckles |
| Neurofibromas (any type) or plexiform neurofibroma | ≥2 neurofibromas or 1 plexiform neurofibroma |
| Optic glioma | 2 or more optic gliomas |
| Sphenoid dysplasia, tibial pseudoarthrosis, or other distinctive bone lesion | 2 or more distinctive bone lesions |
| First-degree relative with a diagnosis of NF1 | 1 or more first-degree relatives with NF1 |

Abbreviation: NF1, Neurofibromatosis type 1.
tumors (MPNSTs), optic nerve gliomas, and pheochromocytomas, among others (see Table 2).

Other non-neoplastic conditions can also occur (see Tables 1 and 2). Neurofibromatosis type I exhibits variable expressivity and can also be associated with a mosaicism-associated presentation, limited to only portions of the body.

What Are the 2 Other Most Common Types of Peripheral Nerve Sheath Tumors?

In addition to neurofibromas, the other common types of peripheral nerve sheath tumors are schwannomas and MPNST. At least a proportion of the cells in all of these tumors show evidence of Schwann cell lineage.

Describe the Clinicopathologic and Genetic Features of Schwannomas

Schwannomas are another type of benign tumor of Schwann cell derivation. They form well-circumscribed, encapsulated masses associated with, but not invading, peripheral nerves. Growth proceeds outside of the perineurium, and clinical effects manifest through compression of adjacent structures.

Describe the Clinicopathologic Features and Genetics of Neurofibromatosis Type 2

Neurofibromatosis type 2 shares a name with its counterpart NF1 due to the overlapping presentation of peripheral nerve tumors; however, the diseases are markedly different. A comparison of the clinical findings in NF1 and NF2 can be found in Table 2. Genetically, NF2 results from anomalies in the NF2 gene on chromosome 22 and loss of the tumor suppressor gene product, merlin. NF2 is an autosomal dominant disorder, approximately half of cases are familial and half are sporadic. Neurofibromatosis type 2 is much less common than NF1 and often presents at a later age (although still in young adulthood, average 18-24 years).

Table 2. Clinicopathologic Features of Neurofibromatosis (NF) 1 and NF2.

| Feature                        | NF1                              | NF2                              |
|--------------------------------|----------------------------------|----------------------------------|
| Inheritance pattern            | Autosomal dominant               | Autosomal dominant               |
| Frequency                      | 1 in 3000                        | 1 in 40,000-50,000               |
| Chromosome/gene/gene product   | 17q11.2/NF1/neurofibromin        | 22q12/NF2/merlin                 |
| Clinical features              | *Café-au-lait macules            | Vestibular schwannomas           |
|                                | *Neurofibromas                   | Meningiomas                      |
|                                | *Axillary/inguinal freckling     | Spinal tumors                    |
|                                | *Optic glioma                    | Neuropathies                     |
|                                | *Iris hamartomas (Lisch nodules) | Ophthalmic                       |
|                                | *Distinctive bone lesions        | Manifestations                   |
|                                | *Family history of NF1 in a first-degree relative | (cataracts, retinal hamartoma, etc) |
| Cognitive and learning deficits|                                  | Cutaneous manifestations         |
| Seizures                       |                                   | (tumors or tumor-like lesions)   |
| Hypertension                   |                                   |                                  |
| MPNST and other soft tissue sarcomas | (rhabdomyosarcoma, GIST, glomus tumor) |                                  |
| Other glial and                |                                  |                                  |
| hamartomatous lesions of the CNS |       |                                  |
| Pheochromocytoma               |                                  |                                  |

Abbreviations: CNS, central nervous system; GIST, gastrointestinal stromal tumor; MPNST, malignant peripheral nerve sheath tumors; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2.

Figure 6. Most of this schwannoma is compact (Antoni A), containing abundant spindled cells, some showing nuclear palisading with intervening “nuclear-free zones” (arrowhead). A few more loosely arranged Antoni B areas are also present (asterisk; hematoxylin and eosin, ×100).

Extradural tumors can also arise in soft tissue with no identifiable associated nerve. Within the dura, schwannomas show a preference for sensory nerves (commonly the trigeminal and vestibulocochlear nerves). The most common intracranial location is the cerebellopontine angle, involving the vestibular branch of cranial nerve VIII, and causing hearing loss and/or tinnitus. In this location, the tumor is often designated as an “acoustic neuroma.” Schwannomas can be sporadic or syndromic, most commonly in association with NF2. In either case, schwannomas are associated with loss of expression of merlin, the NF2 gene product. Merlin normally interacts with the actin cytoskeleton to control growth factor receptor expression on the cell surface. Histologically, schwannomas usually contain densely compact foci, called Antoni A areas, and paler, more loosely arranged portions known as Antoni B areas (Figure 6). Verocay bodies may be seen in the Antoni A areas, showing rows of palisaded nuclei with intervening eosinophilic cytoplasm. The myxoid stroma in Antoni B areas can form microcysts. A capsule and hyalinized vessels are also typical of schwannomas.
frequently associated with neurofibromas, but schwannomas are common (classically as bilateral “acoustic” tumors on cranial nerve VIII), as are central nervous system tumors (especially multiple meningiomas). Multiple schwannomas can also be encountered in patients with syndromes other than NF2, including schwannomatosis and Carney complex.1

Describe the Clinicopathologic Features of Malignant Peripheral Nerve Sheath Tumors. How Are These Tumors Related to Neurofibromas?

As the name implies, malignant peripheral nerve sheath tumors are malignant and are often high grade. They can be sporadic or transform from a plexiform neurofibroma in an NF1 patient. These tumors may be poorly circumscribed and invade surrounding tissue. Histologically, the appearance can be variable. Malignant peripheral nerve sheath tumor is typically hypercellular with cytologic atypia, abundant mitotic figures, and sometimes necrosis. The cells are often spindled and arranged in fascicles (Figure 7A and B).1,3 Malignant peripheral nerve sheath tumors are sometimes difficult to diagnose due to their lack of differentiation. One interesting occurrence is that some of these tumors can show differentiation toward other tissue types (eg, rhabdomyoblasts, glands, cartilage, etc). Genetic analysis often shows numerous changes, including chromosomal rearrangements, gains, and losses.1 Treatment depends on the tumor location as well as other patient characteristics.

Teaching Points

- Peripheral nerve sheath tumors show evidence of Schwann cell differentiation. The 3 most common types are neurofibroma, schwannoma, and MPNST.
- The 3 types of neurofibroma based on morphology are localized cutaneous neurofibroma (most cases unassociated with NF1), diffuse neurofibroma (more commonly associated with NF1), and plexiform neurofibroma (only found in NF1).
- Neurofibromas are well circumscribed and are composed of neoplastic Schwann cells as well as a mixture of other cell types.
- Schwannomas are another type of benign peripheral nerve sheath tumor and can be associated with NF2, especially when involving cranial nerve VIII bilaterally.
- Schwannomas are also well circumscribed and are composed of Schwann cells.
- Malignant peripheral nerve sheath tumors are often high-grade neoplasms and can arise either spontaneously or from malignant transformation of a plexiform neurofibroma.
- Malignant peripheral nerve sheath tumors can be poorly circumscribed and infiltrative and are often composed of mitotically active spindle cells.
- Neurofibromatosis type 1 is a relatively common autosomal dominant disorder associated with neurofibromas, cafe au lait macules, axillary/inguinal freckles, and optic gliomas.
- Neurofibromatosis type 2 is less common and associated with schwannomas, central nervous system tumors, and ophthalmic disease.

Authors’ Note

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ORCID iD
Alison R. Huppmann https://orcid.org/0000-0003-0739-1721

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