Inflammatory myofibroblastic tumor of the ulnar nerve

Case report and review of the literature

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Inflammatory myofibroblastic tumors with involvement of cranial and peripheral nerves are exceedingly rare. The authors present the case of a 67-year-old man with an inflammatory myofibroblastic tumor of the left ulnar nerve, which was identified intraoperatively and mimicked a malignant neoplastic lesion. Histopathological examination revealed loosely structured fibrous tissue and collagen deposits intermingled with patchy infiltrates of lymphocytes, plasma cells, and histiocytes penetrating the endo- and epineurium of the affected nerve fascicles. There was strong expression of vimentin and actin in spindle cells throughout the lesion. The histiocytes were CD68- and major histocompatibility complex class II-positive, but lacked CD1a expression. A review of the literature revealed nine histopathologically confirmed cases of inflammatory myofibroblastic tumors involving peripheral or cranial nerves in which slight differences in histopathological features and surgical management were found, which are discussed here.

**Key Words**  • inflammatory myofibroblastic tumor  • pseudotumor  • plasma cell granuloma  • peripheral nervous system

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**Case Report**

**History and Examination.** We report the case of a 67-year-old man in whom progressive pain of the left forearm had been occurring intermittently for 3 months. He had a history of painful angina pectoris on exertion, arterial hypertension, and heartburn. Neurological examination revealed pressure pain on the volar side, a positive Hoffmann–Tinel sign, dysesthesia of the fifth digit and the ulnar part of the fourth digit, and a paresis of the muscles innervated by the ulnar nerve. During electrophysiological examination an acute inflammatory lesion was proposed as the diagnosis. Magnetic resonance imaging of the left forearm revealed a fusiform enlargement of the distal ulnar nerve.

**Operation.** On surgical exploration, adherence of the nerve and artery to the surrounding tissue was observed. The ulnar nerve appeared diffusely enlarged. An attempted epineurectomy failed due to massive infiltration of the nerve, which was lacking healthy fascicles (Fig. 1). Intraoperative electrostimulation yielded insufficient response of the innervated muscles. An intraoperative neuropathological diagnosis of a highly cellular mass with polymorphic cell elements was compatible with a malignant tumor. Therefore, the 6-cm-long macroscopically infiltrated segment was resected and replaced using a triplicate sural nerve reconstruction. After resection of the diseased part of

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Abbreviations used in this paper: ALK = anaplastic lymphoma kinase; EBV = Epstein–Barr virus; EMA = epithelial membrane antigen; HSV = herpes simplex virus; MHC = major histocompatibility complex.
the ulnar nerve, a 6-cm-long defect resulted. Because the diameter of the ulnar nerve was three times larger than the sural nerve transplants, three sural transplants placed parallel were used for reconstruction of the full diameter of the nerve.

**Postoperative Course.** Postoperative recovery was uneventful, and the preoperative paresis and dysesthesia of the ulnar region was unchanged when the patient was discharged. Follow-up examinations including clinical and electrophysiological evaluations with myography and neurography were performed 5, 9, and 12 months postoperatively. Five months after the operation the clinical examination demonstrated a positive Hoffmann–Tinel sign several centimeters distal to the location of the nerve reconstruction, corresponding to sprouting nerve fibers. The electromyographic study of the abductor digiti minimi muscle of the hand demonstrated the beginning of reinnervation.

**Pathological Findings.** Macroscopic evaluation of the formalin-fixed tissue specimens showed a gray, brown, firm rather than elastic fusiform mass. Gross hemorrhage and necrosis were absent. The 4-μm-thick formalin-fixed paraffin sections were routinely stained with Luxol fast blue (Fig. 2A, H & E (Fig. 2B and D), elastica van Gieson (Fig. 2C), reticulin, and Giemsa (Fig. 2E and F). Additional stains included Gram and Grocott. Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tissue by using the streptavidin–biotin peroxidase complex method and monoclonal antibodies directed against S100 (Fig. 3A), CD45 (Fig. 3B), CD1a and CD3 (Fig. 3C), CD4 and CD8 (Fig. 3D), CD20 (Fig. 3E), CD68 and CD138 (Fig. 3F), MHC class II (Fig. 3G), neurofilament, synaptophysin, desmin, sarcomeric actin, c-Kit, p53, HSV1 & -2, and monoclonal antibodies directed against S100 (Fig. 3A), MHC class II, NF, EMA, CK, SMA, synaptophysin, desmin, sarcomeric actin, c-Kit, p53, HSV1 & -2, and the proliferation marker MIB-1 (Fig. 3H).

On histological examination the lesion consisted primarily of poorly circumscribed fibrous tissue and collagen deposits interspersed with patchy infiltrates of lymphocytes and plasma cells. Histiocytes consisted of larger eosinophilic cells with elongated nuclei. In addition, perivascular lymphocellular infiltrates were present as well as small foci of necrosis with a few hypersegmented granulocytes. The nerve fascicles were surrounded by chronically inflammatory tissue infiltrating the endo- and epineurium. After addition of Luxol fast blue stain, a decrease of myelin in the nerve fibers could be observed, although results of immunohistochemical staining for EMA, neurofilament, and S100 were in the range of normal. No cytological atypia was present. The intermingled CD45-positive inflammatory cells consisted mostly of B cells, 5 to 10% CD5-positive

<table>
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<tr>
<th>Authors &amp; Year</th>
<th>Patient Age (yrs), Sex</th>
<th>Tumor Location</th>
<th>Immunostaining Methods</th>
<th>Histological Findings</th>
<th>Extent of Resection</th>
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<tr>
<td>Keen et al., 1986</td>
<td>55, M</td>
<td>mandibular nerve</td>
<td>none</td>
<td>epidural lesion surrounded by fibrotic granulation tissue w/ chronic inflammation</td>
<td>resection of mandibular nerve</td>
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<tr>
<td>Yanagihara et al., 1991</td>
<td>41, M</td>
<td>facial nerve</td>
<td>none</td>
<td>epineural lesion surrounded by fibrous granulation tissue</td>
<td>resection of mass &amp; nerve</td>
</tr>
<tr>
<td>Wiseman et al., 1995</td>
<td>4, M</td>
<td>lt facial nerve</td>
<td>$100</td>
<td>lymphocytes, plasma cells, histiocytes; accompanied by oitis media</td>
<td>2 wks postbiopsy, excision of the tumor sparing the nerve</td>
</tr>
<tr>
<td>Weiland et al., 1996</td>
<td>35, M</td>
<td>fusiform sciatic nerve mass</td>
<td>S100, NF, EMA, CD2, CD3, CD5, CD7, CD20, CD22, kappa, lambda</td>
<td>patchy infiltrates of lymphocytes &amp; plasma cells, myelin loss, mixed B- &amp; T-cell type, no light chain restriction</td>
<td>resection of epineurial mass</td>
</tr>
<tr>
<td>18, F</td>
<td>enlargement, radial nerve</td>
<td>$100, NF, EMA, CD20, CD45, CD68</td>
<td>clustered, partially multinucleated histiocytes ($100), T &amp; B lymphocytes</td>
<td>resection of epineurial nerve mass sparing nerve fascicles</td>
<td></td>
</tr>
<tr>
<td>Rubio et al., 1997</td>
<td>69, M</td>
<td>rt facial nerve (mastoid antrum)</td>
<td>kappa, lambda</td>
<td>plasma cells, Russell bodies, no nerve fascicles</td>
<td>removal of tumor mass &amp; facial nerve exposure</td>
</tr>
<tr>
<td>Beer et al., 1998</td>
<td>41, M</td>
<td>lt greater auricular nerve</td>
<td>$100, EMA, NF</td>
<td>follicular lymphoid hyperplasia w/ germinal centers, few plasma cells, no multinucleated giant cells</td>
<td>resection w/ segment of nerve</td>
</tr>
<tr>
<td>Perez-Lopez et al., 2001</td>
<td>27, F</td>
<td>fusiform mass, rt median nerve</td>
<td>IgM</td>
<td>heterogeneous lymphoid infiltration, predominantly epineurial, mononuclear cells, T lymphocytes, plasmacytoid cells</td>
<td>partial resection of fascicles demonstrating the most infiltration</td>
</tr>
<tr>
<td>Jung et al., 2006</td>
<td>52, M</td>
<td>origin from 5th nerve root &amp; adherent to 4th cranial nerve</td>
<td>CD45, S100, EBV, HSV</td>
<td>fibrovascular tissue w/ infiltration of plasma cells &amp; lymphocytes, hemorrhage</td>
<td>almost total tumor resection, including 4th cranial nerve</td>
</tr>
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<td>present study</td>
<td>67, M</td>
<td>lt ulnar nerve</td>
<td>S100, CD45, CD1a, CD3, CD4, CD8, CD20, CD68, CD138, MHC-II, NF, EMA, CK, SMA, synaptophysin, desmin, sarcomeric actin, c-Kit, p53, HSV1 &amp; -2</td>
<td>patchy infiltrates of lymphocytes &amp; plasma cells &amp; histiocytes, myelin loss, B cells predominating over T cells</td>
<td>resection of mass &amp; segment of nerve</td>
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* CK = cytokeratin; MHC-II = MHC class II; IgM = immunoglobulin M; NF = neurofilament; SMA = smooth-muscle actin.
cells, and 10 to 20% T cells consisting of a higher ratio of CD4-positive to CD8-positive cells. In addition there was staining of a few CD138-positive plasma cells. The histiocytes were CD68- and MHC class II–positive, but lacked CD1a expression. The S100 protein was only present in a few larger cells. The proliferation marker MIB-1 (Ki 67) was only slightly elevated in the infiltrating cells. No p53 or c-Kit (CD117) expression was seen in the tumor. Immunohistochemical staining for pan-cytokeratin and desmin yielded negative results, whereas diffuse expression of vimentin and sarcomeric actin, and focal expression of smooth-muscle actin were seen. There was no sign of light chain restriction in immunohistochemical testing for kappa and lambda. No immunohistochemical expression of ALK was observed. No cytoplasmic expression of EBV, cytomegalovirus, or HSV1 and -2 antigens was detected.

Discussion

Inflammatory myofibroblastic tumors represent a diagnostic and clinical challenge. The vast majority of localized nerve enlargements are of a benign neoplastic nature, notably in such lesions as schwannomas and neurofibromas, although they sometimes transform into malignant peripheral nerve sheath tumors. Intraural perineuriomas may form segmental “pseudo–onion bulbs” composed of clonally proliferating perineural cells surrounding myelinated or nonmyelinated nerve fibers.12 We observed no such signs of a hypertrophic neuropathy. Solitary peripheral nerve lymphomas, also known as neurolymphomatosis, consist mainly of infiltrating, highly proliferative B cells displaying cytological features of malignancy and sparing the perineurium;10 our case lacked these features. In addition, immunohistochemical staining for kappa and lambda showed no evidence of light chain restriction.

Localized enlargement of a peripheral nerve also may result from infectious or reactive processes. Especially in the tuberculoid form of leprosy neuropathy, an endoneurial proliferation of fibroblasts differentiating into perineurial cells results in a segmental enlargement of the peripheral nerve.12 Other inflammatory lesions such as sarcoidosis and Langerhans cell histiocytosis also might display nonspecific neuroradiological and clinical findings. On immunohistochemical examination these lesions stain positively for S100 antigen, and histiocytosis also stains positively for CD1a. Although rarely seen in the central nervous system, the lymphoproliferative disorder Rosai–Dorfman disease is one important differential diagnosis.13 In the peripheral nervous system, one case showing entrapment of the ulnar nerve without nodal involvement has been reported in the literature.15

Amyloid deposits of the immunoglobulin light chain lambda subtype (classified as AL-κ) might displace nerve fibers and form a pseudotumor of the peripheral nerve.3 No hyaline, eosinophilic, Congo red–staining inclusions were seen in our case. Hereditary diseases like Charcot-Marie-Tooth or Dejerine–Sottas disease might form histologically onion-bulb structures, although their hypertrophic nature is most likely to affect more than one nerve.16 Other possibilities, including acute infection of the nerve, could be exclud-
expression of ALK affecting the central nervous system has been described.\textsuperscript{14} Such cytogenetic changes combined with ALK expression, however, are seldom observed in patients older than 40 years of age.\textsuperscript{5,22} Likewise, our patient showed no expression of ALK. It remains to be examined whether the ALK-positive inflammatory pseudotumors represent a subgroup with a worse prognosis or are in fact a separate entity that is a rather benign lymphoproliferative disorder. The long-term observations even in cases of incomplete resection do not support the latter theory.

With the presence of the EBV genome in some cases,\textsuperscript{13,17} an abnormally prolonged postinfectious reparative process had been proposed. This may result not only from viral infections but from other causes as well, as in one case affecting the facial nerve that has been associated with a previous purulent otitis media.\textsuperscript{34} The presence of signs of systemic inflammation in 15 to 30% of examined cases supports this hypothesis.\textsuperscript{23} A similar pathogenesis has been proposed for Castleman disease, which may also appear unicentric, and in a plasma cell–rich variant. Hypotheses include overproduction of interleukin-6 and previous human HSV type 8 infection.\textsuperscript{6} In our case there were no signs of bacterial or fungal infection after testing with the appropriate stains. Immunohistochemical staining for viral antigens to EBV, cytomegalovirus, HSV1, and HSV2 also yielded negative results.

In some cases vascular changes are seen as causative for inflammatory myofibroblastic tumors. The accumulation of mononuclear cells combined with fibrosis of vessels might result in reduced perfusion and enhance tissue destruction,\textsuperscript{14} thus triggering further reactive processes. In cases with extensive vessel infiltration, hemorrhage might be seen.\textsuperscript{17} Additional perivascular infiltrates consisting of inflammatory cells together with few hemosiderin deposits, a sign of very discrete older hemorrhages, were seen in our case. Nevertheless, it cannot be ruled out that vascular changes might be reactive by nature due to long-term regressive changes associated with the presence of chronic inflammation. In a published case of a tumor of the pterygomaxillary space, occluding fibrosis of medium-sized vessels is described by the authors of the study.\textsuperscript{19} Although there was a reported history of dental injections in this area, no foreign material or granulomatous reaction was seen. In our case a reactive process cannot be completely ruled out because it is possible that a previously placed intravenous cannula, which is not uncommon in the ulnar region, might have induced the inflammatory myofibroblastic tumor, either by direct trauma or by the substances injected.

Therapeutic approaches include resection of a segment of the nerve or removal of the epineurial mass, sparing the nerve. Regrowth of the lesion was observed in one case, affecting the proximal and distal nerve stumps 2 years later.\textsuperscript{12,28} In contrast, in a case with only partial resection of the most affected nerve fascicles, no tumor regrowth was found within the follow-up period of 8 years, and progressive reinnervation of the distal muscles has also been demonstrated.\textsuperscript{25} The efficacy of chemotherapy and radiation therapy is not yet proven.\textsuperscript{9}

**Conclusions**

Inflammatory myofibroblastic tumors pose an intraoperative challenge because the pathological diagnosis is not
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obvious from assessments of frozen sections of specimens, yet the lesion has a clinically malignant appearance. Therefore, an individualized approach is necessary, in which surgical management should be used only to resect the mass. As in our case, however, sparing of the nerves is not always possible (see Table 1: five of nine cases reported) and the option of a nerve reconstruction needs to be taken into consideration.

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References

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