Pathology Quiz Case 1: Diagnosis

**Diagnosis:** Nasopharyngeal tuberculosis

Tuberculosis in the head and neck region is often diagnosed, and several presentations of head and neck tuberculosis have been described. However, solitary nasopharyngeal tuberculosis is an uncommon entity and, to our knowledge, has rarely been reported in the literature. A 10-year retrospective study among 1315 tuberculosis cases in Bradford, England, resulted in 128 patients with head and neck tuberculosis. Most of these patients (n = 111 [87%]) had cervical tubulifus lymphadenitis. Only 1 patient (a 36-year-old Asian man) presented with bilateral middle ear effusions and was diagnosed as having nasopharyngeal tuberculosis after nasal biopsy. Eighty-nine percent of the patients (n = 114) were of Asian origin, and 10.2% (n = 13) were white. Nalini and Vinayak described 117 patients with head and neck tuberculosis, 111 of whom (95%) were diagnosed as having cervical lymphadenopathy. They also reported cases of tuberculosis of the larynx, oropharynx, cervical spine, and ear. Nasopharyngeal tuberculosis was not reported.

Most of the available literature about nasopharyngeal tuberculosis involves series of cases and individual case reports of patients with varying symptoms, of which cervical lymphadenopathy is the most common. Waldron et al described 10 patients with nasopharyngeal tuberculosis between 1985 and 1989. Seven patients presented with enlarged cervical nodes. Other symptoms were nasal obstruction, weight loss, cough, decreased hearing, secretory otitis media, and general malaise. In 8 cases, the chest x-ray films showed no abnormalities.

Srirompotong et al published a retrospective study involving 23 patients in Thailand with nasopharyngeal tuberculosis between 1991 and 2000. Again, cervical lymphadenopathy was most commonly reported as the main symptom (91.3%). Other symptoms were weight loss and fever (30.4%), epistaxis (13.1%), nasal obstruction (8.7%), and hearing loss (4.3%). The observed nasopharyngeal abnormalities consisted of an irregular surface, ulcerations, or a nasopharyngeal mass. A chest x-ray film that was suggestive of pulmonary tuberculosis was found in 44.4% of the cases. Tse et al reported 17 cases of nasopharyngeal tuberculosis. Ten patients presented with cervical lymphadenopathy and 2 patients with hearing loss. Other symptoms were otalgia, tinnitus, nasal obstruction, and postnasal drip. Two patients also had fever, night sweats, and weight loss. Chan et al described 3 patients who developed solitary nasopharyngeal tuberculosis after they completed radiotherapy for nasopharyngeal carcinomas. They raised the possibility of local tissue damage after irradiation creating a portal of entry for infection through the inhalation of tuberculosis. It should be pointed out that the patients lived in geographical areas with a high incidence of tuberculosis.

In the absence of cervical lymphadenopathy or other evident clinical abnormalities, it is difficult to discriminate between nasopharyngeal tuberculosis and a malignant nasopharyngeal tumor. One patient without cervical lymphadenopathy and normal findings on the chest x-ray film presented with snoring as the only complaint. Only mucosal edema and hyperemia of the nasopharynx were found. Koktener and Koktener described a patient who presented with headache as the only symptom. This patient was diagnosed as having nasopharyngeal tuberculosis after a nonspecific nasopharyngeal lesion was observed on magnetic resonance imaging, followed by biopsy. King et al described 2 patterns that could be used to identify nasopharyngeal tuberculosis on magnetic resonance images: polypoid mass of the adenoids and a diffuse thickening of the mucosal wall of the nasopharynx. However, only 3 cases were included and compared with available literature.

Our 92-year-old white patient presented with minor dysphagia-related symptoms. An observed ulcerating and granulating nasopharyngeal lesion was clinically highly suggestive of a nasopharyngeal carcinoma. Retrospectively, our patient’s medical history revealed long-term contact with a patient who had pulmonary tuberculosis. The minor irregularity and mild enhanced signal intensity that were observed on the T2-weighted magnetic resonance image were not specific for either inflammation or a nasopharyngeal carcinoma.

In the absence of cervical lymphadenopathy and abnormal findings on the chest-x-ray film, histopathologic examination of the nasopharyngeal lesion showed an active granulomatous infection without evidence of malignant tissue. The histologic features can be confused with those of several pathologic entities. Infection with *Mycobacterium tuberculosis* is probably the best-known cause of a necrotizing granulomatous inflammation. Similar histologic changes can also be identified in infections with nontuberculous mycobacteria, although necrosis is not often present in those cases. The granulomas found in sarcoidosis are mostly well organized, with minimal or no necrosis. Sometimes, Schaumann and asteroid bodies are present. A granulomatous inflammation can also be seen in vasculitides, such as Wegener granulomatosis or Churg-Strauss syndrome.

In this case, the multiple foci of necrosis were not typically located in the center of the granulomas, which would be expected in a classic tuberculosis case. A Ziehl-Neelsen stain was negative for acid-fast bacilli. Nevertheless, neither the atypically located necrosis nor the negative result on the Ziehl-Neelsen stain could exclude the presence of *M tuberculosis*. Microbiological cultures of the mouth, nose, and lesion showed only common flora. An additional periodic acid–Schiff diastase stain did not show fungi or spores. Finally, molecular polymerase chain reaction analysis was performed on the formalin-fixed, paraffin-embedded biopsy material. The findings confirmed infection with *M tuberculosis*. Computed tomography with contrast showed no other signs of systemic tuberculosis.

Standard quadruple therapy was limited to isoniazid, 300 mg/d, and rifampicin, 600 mg/d, because of possible liver enzyme disorders. After the first month of therapy, the nasopharyngeal lesion was substantially reduced. The recovery of the patient was monitored during a monthly checkup at our outpatient department. The
Pathology Quiz Case 2: Diagnosis

Diagnosis: Merkel cell carcinoma (MCC) of the left auricle

Merkel cell carcinoma, which is an uncommon, aggressive cutaneous neoplasm, was first described in 1972. Although MCCs were originally thought to originate from neuroendocrine mechanoreceptor cells, it is now believed that they are derived from pluripotent neural crest cells. Nearly half of all MCCs present in the head and neck area. Facial areas, including the cheeks, nose, mouth, and eyelids, are the most common sites, while auricular MCC is extremely rare. Merkel cell carcinoma exhibits rapid growth and aggressive lymphatic spread, and 25% of patients will have local or distant spread at initial presentation. An additional 30% will develop local or distant spread during the disease course. On physical examination, MCC lesions appear as pink or violaceous subcutaneous nodules. Ulceration is a rare finding.

Although rare, the incidence of MCC has tripled in the past 15 years. This increase may be the result of improved recognition as well as of an aging population and more sun exposure. Risk factors include age (average age at diagnosis, 70 years), male sex, sun exposure, and immunosuppression. Merkel cell carcinoma seems to be disproportionately associated with other neoplasms, including skin, hematologic, ovarian, and breast adenocarcinomas.

The pathogenesis of MCC is multifactorial. Mast cells may mediate several aspects of neoplastic proliferation through several mechanisms, including immunosuppression, angiogenesis stimulation, extracellular matrix degradation, and mitogenesis. The presence of mast cells on microscopic examination of the MCCs can be correlated with an increased risk of death. Merkel cell polyomavirus has been found in a high percentage of MCCs in several series. Merkel cell polyomavirus integrates into the genome, and 2 oncogenes, LT and ST, are expressed. Acting similarly to the human papillomavirus E6 and E7 proteins, LT inactivates p53 and pRb; ST disrupts a protein phosphatase complex that has been implicated in cellular adhesion. Also, deletions and unbalanced translocations have been identified in the short arm of chromosome 1.

On microscopic examination, MCC exhibits small round cells arranged in sheets and trabeculae. Infiltration into surrounding dermal lymphatics is common and indicative of the aggressive nature of this disease. Cytoplasmic granules show similarities to cells of neuroendocrine and amine precursor uptake decarboxylation cell lineage. Intercellular junctions, vesicular nuclei with fine chromatin, high nuclear to cytoplasm ratio, and spiky processes are all characteristic cytologic features. It is common for samples to exhibit large numbers of mitotic figures and numerous apoptotic cells. Immunohistochemical analysis can aid the pathologic diagnosis, with MCC demonstrating characteristic perinuclear dotlike immunopositivity for CK20. Often morphologically similar to metastatic small cell carcinoma of the lung, MCC notably lacks a recently identified marker known as achaete-scute complex–like 1. Furthermore, small cell carcinoma of the lung is typically positive for thyroid transcription factor 1, whereas MCC is negative. The absence of S-100 protein and homatropine methylbromide helps rule out malignant melanoma. Immunohistochemical analysis can also serve a prognostic role, with p63 expression associated with (1) a more aggressive clinical course; (2) nuclear expression of the antiapoptotic protein survivin, which is associated with higher mortality and rates of metastasis; and (3) overexpression of matrix-metalloprotein 7, which has been shown to be associated with increased metastasis. Other pathologic characteristics associated with a worse prognosis include lymphocytic infiltration and a high mitotic index.

After a pathologic diagnosis, presurgical staging should include a clinical examination and may include a PET scan. A PET scan may contribute useful information about the presence of metastatic lesions, but normal findings on the PET scan do not rule out metastatic disease. Computed tomography is not accurate for detecting nodal disease. Wide local excision with 2- to 3-cm margins is the initial treatment of choice. However, such large margins are often difficult to obtain in the head and neck area. With respect to auricular lesions, auriclectomy may be nec-