Chapter 75: Beningn and Malignant Neoplasms of the Nasopharynx

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Benign Neoplasms

The nasopharynx or "epipharynx" is the cephalic end of the tubular aerodigestive tract. Various epithelia - keratinized and nonkeratinized squamous, pseudostratified, ciliated, and columnar - make up its internal surface, along with glandular and lymphoid tissues. Deeper tissues are composed of connective tissue, including fascia and muscle. Therefore one can expect occasionally to encounter the diversity of benign tumors that arise from epithelia and lymphoid, glandular, and connective tissue.

Benign tumors of the nasopharynx are rare. One will occasionally see fibromyxomatous polyps, pedunculated fibromas, papillomas, and teratomas, as well as extracranial tumorlike entities that may present in the nasopharynx - craniopharyngiomas, extracranial meningiomas, encephaloceles, hemangiomas, and chordomas (not always benign); to this list should be added antral-choanal polyps because they often present as nasopharyngeal "tumors". In contrast, other benign tumorlike neoplasms such as adenoids, Tornwaldt's cysts of the pharyngeal bursa, choanal polyps, and mucosal cysts are common.

No recent incidence or prevalence data list epithelial tumors; however, Fu and Perzin (1974) reviewed the records from a 35-year period at the laboratory of surgical pathology of the Presbyterian Hospital in New York City for a clinicopathologic study of *nonepithelial* tumors of the nose, paranasal sinuses and nasopharynx. The histologic classification and distribution are shown in Table 75-1. The number and distribution of tumors in the nasopharynx alone were not noted, except for vascular tumors; as expected, angiofibromas were the most common benign tumors, and all 38 occurred in the nasopharynx. A detailed discussion of this tumor follows.

Angiofibroma

Angiofibroma is a benign tumor that affects young males. The triad of nasal obstruction, a nasopharyngeal mass, and recurrent epistaxis usually indicates the presence of the neoplasm, which is morphologically benign but aggressive and destructive (Neel et al, 1973). Although angiofibromas are the most common benign tumors of the nasopharynx, they account for less than 0.05% of head and neck tumors (Lee and Sessions, 1980; Waldman et al, 1981). The low frequency of occurrence has made it difficult for individuals or institutions to accumulate a sufficiently large series for an in-depth prospective or retrospective study. The term *juvenile angiofibroma* or simply *angiofibroma* is most appropriate because the tumor is not often limited to the nasopharynx and usually has extensions, for example, into the nose, paranasal sinuses, pterygomaxillary fossa, and other adjacent regions (Bremer et al, 1986; Neel et al, 1973; Sessions and Humphreys, 1984). The term *juvenile* is inaccurate because the neoplasm occurs in older patients too.

Although angiofibromas are classified as benign, they may grow considerably and cause significant structural and functional damage. They often erode bone and push into and through regional structures. Many of the grow insidiously to a substantial size, sometimes into

the cranium, before symptoms occur; the symptoms are often attributed to more common problems before an accurate diagnosis is established (Batsakis, 1979; Biller, 1978; Bremer et al, 1986; Jafek et al, 1979; Jones et al, 1986; Neel et al, 1973; Roberson et al, 1972; Standefer et al, 1983). Surgical therapy is the treatment recommended by most authors, and the tumors are a challenge for even the most experienced head and neck surgeons.

Important issues relate to the choice of diagnostic procedures, adjunctive measures, surgical approach, and role of radiation therapy (Bremer et al, 1986; Jones et al, 1986; Neel et al, 1973).

Gross and histologic morphology

Angiofibromas are pale blue, smooth, and often lobulated. The overlying mucosa is rarely ulcerated unless the patient has had previous biopsy or therapy (Neel et al, 1973). Often, dry blood and mucus may be on the surface of the tumor.

Light microscopy reveals angiofibroma to be benign and composed of spindle or stellate fibrocytes in various connective tissue stroma. The two striking microscopic features, a fibrostroma and a rich vascular network, may vary in their respective patterns (Batsakis, 1979; Neel et al, 1973). Vascular channels may be small and of a capillary size or very large and of a venous size; the channels are lined with endothelial cells that lie directly against stromal cells. There is no intervening smooth muscle between these two cell types, and this feature undoubtedly contributes to the capacity for massive bleeding that occurs with either biopsy or removal (Fig. 75-1). Batsakis (1979) noted that the classic histologic appearance of the tumor is generally found in the interior portions; some investigators believe that surface biopsy specimens of the tumor mass may be misleading.

Clinical findings and point of origin

In a study of 150 patients at the Mayo Clinic, all patients were white males (Bremer et al, 1986) whose ages ranged from 7 to 29 years at diagnosis (median age, 15 years). No angiofibromas occurred in patients older than 30 years or in females. The tumors were not more "aggressive" nor more likely to show intracranial spread in younger patients.

Nasal obstruction and epistaxis occurred in more than 80% of the patients (Table 75-2). The typical patient was a young boy who had had occasional expistaxis and nasal obstruction. There may have been some bulging of the face or eye, and examination showed a pale blue, smooth mass in the nasopharynx and often in the posterior aspect of the nose. In most patients the tumor was located on the side of the nasopharynx. This observation confirms the surgical observation that the specific point of origin is at the posterolateral wall of the roof of the nose where the sphenoid process of the palatine bone meets the horizontal ala of the vomer and the root of the pterygoid process of the sphenoid bone (Fig. 75-2) (Neel et al, 1973). This junction forms a superior margin of the sphenopalatine foramen, and the ethmoid crest or attachment of the posterior end of the middle turbinate lies on or above the foramen. An understanding of the point of origin of the tumor helps to explain the pathways of extension of the tumor. From the point of origin, the tumor may extend into the nose, the nasopharynx, the paranasal sinuses, the temporal fossa, the infratemporal fossa, and the cranium (Fig. 75-3) (Bremer et al, 1986; Neel et al, 1973).

Diagnostic evaluation

The diagnosis is based on a thorough history, physical examination, and roentgenologic studies. It is interesting that patients may be observed for significant periods with diagnoses such as sinusitis, rhinitis, or antral choanal polyps. During the past 40 years, the duration of symptoms before treatment has decreased from a mean of 20 months to a mean of 6 months (Bremer et al, 1986). This decrease probably reflects a greater awareness of this rare tumor and improved diagnostic methods.

The trend in the application of roentgenography for diagnosis has changed from plain sinus roentgenograms to tomograms, to a combination of tomograms and computed tomographic scans of the head, and, finally, to a computed tomographic scan of the head alone, with and without contrast medium. The roentgenographic findings that are considered classic for angiofibroma are combinations of the following: (1) nasopharyngeal mass, (2) anterior bowing of the posterior wall of the antrum, (3) erosion of the sphenoid bone, (4) erosion of the hard palate, (5) erosion of the medial wall of the maxillary sinus, amd (6) displacement of the nasal septum. Anterior bowing of the posterior wall of the maxillary sinus, the Holman-Miller sign, has been considered pathognomonic of angiofibroma, but other lesions such as fibromyxomatous polyps may rarely cause similar roentgenographic findings (Holman and Miller, 1965; Neel et al, 1973; Shaffer et al, 1978). As noted, computed tomography of the head with contrast medium has supplanted hypocycloidal tomography for the diagnosis of angiofibroma. Magnetic resonance imaging is indicated in some patients, particularly in those who may have intracranial extension and in those whose soft-tissue planes require clearer delineation.

Angiography has been unnecessary in most patients (Bremer et al, 1986; Jones et al, 1986). It has been used for cases in which intracranial extension has been suspected or when the diagnosis remains in question, usually for patients in whom previous treatment has failed. The technique and technology of angiography have improved a great deal in recent years; however, there are risks associated with angiography, especially when embolization is used (Biller, 1978; Neel et al, 1973; Roberson et al, 1972; Ward, 1983; Ward et al, 1974).

Computed tomography has improved our capacity to define the extent of the tumor clearly and safely. Computed tomographic scans define precisely the extent of the tumor, bony destruction, sinus involvement, and other extensions. A computed tomographic scan of the head is now an integral part of the preoperative diagnostic evaluation.

Finally, at the time of planned surgical resection, a biopsy of the tumor is performed with the patient under general anesthesia, to establish a definitive diagnosis; however, the need for biopsy has been challenged (Sessions and Humphreys, 1984).

Clinical staging systems

Sessions et al (1981) proposed a system that is based on tumor location and extension to stage angiofibromas. They proposed that the computed tomographic scan should be used for the standardized reporting and staging of patients with angiofibroma ater a clinical investigation in which angiofibroma is suspected. A description of the stages follows:

I, Tumor limited to posterior nares or nasopharyngeal vault

IIA, Minimal lateral extension through sphenopalatine forament into the pterygomaxillary fossa

IIB, Filling of pterygomaxillary fossa displacing the posterior wall of antrum, or superior extension eroding bone of the orbit

IIC, Extension through pterygomaxillary fossa into cheek and temporal fossa

III, Intracranial extension.

From the surgeon's viewpoint, stages IIC and III, the extensive tumors at the skull base and those with intracranial extension, are the most difficult to treat. Indeed, three fourths of recurrences occur in the stage III grouping (Table 75-3).

Chandler et al (1984) described a four-stage system.

Management

Various surgical approaches have been described recently: the facial degloving procedure and the extensive intracranial and extracranial approaches (Chandler et al, 1984; Jafek et al, 1979; Standefer et al, 1983). The approach used may depend on the surgeon's experience with a given technique. However, the lateral rhinotomy approach and its variations is the most direct route to the body of the tumor and is versatile so that the surgeon can reach all the extensions of the tumor (Bremer et al, 1986; Jones et al, 1986; Neel et al, 1973). Other surgical approaches provide limited, inadequate exposure, as noted in a detailed review of the various approaches (Neel et al, 1973).

Given the point of origin of the tumor (described above), it is clear that the lateral rhinotomy incision provides an excellent approach to the tumor. The incision can be extended down the center of the upper lip when lateral exposure is required beyond the infraorbital foramen (Fig. 75-4); this method provides better superior and lateral exposure than does the facial degloving approach. The skin incision begins or ends within or just beneath the medial aspect of the brow and curves downward to within 5 mm of the inner canthus. The portion of the incision near the depression of the inner canthus should be curved so that a web of scar does not form. It then curves forward and downward on the side of the nose *midway* between the nasal dorsum and the nasal facial angle. It is carried down through the periosteum. The incision is carried down the side of the nose to the base of the ala, where it may terminate if the rhinotomy is limited. Because most angiofibromas extend beyond the nose and the nasopharynx, the incision is continued around the base of the nose to the base of the columella, where it turns and runs down the center of the upper lip. The incision on the mucosal surface of the upper lip has a "Z" incorporated into it. The incision reaches the depth of the alveolobuccal sulcus and continues in the sulcus to the maxillary tuberosity.

Once the incision is completed, the underlying bone must be adequately removed to get good exposure, and this should be completed before the tumor is touched. The nasal bone is removed to the midline and to its junction with the frontal bone. The frontal process of the maxilla and the facial surface of the maxilla are removed. A small margin of bone around the infraorbital nerve at the level of the foramen is preserved. By this time, the antrum is opened and the posterior wall is inspected. If the antrum is bulging forward excessively, more exposure is needed. The infratemporal surface of the maxilla should be removed along with

the eggshell of bone on the posterior wall of the antrum. The terminal branches of the internal maxillary artery usually can be identified and are ligated, clipped, or electrocoagulated. The internal maxillary artery is invariably the main source of blood supply to the tumor.

As Neel et al (1973) noted in a detailed description of the surgical procedure, the tumor can be extracted from the pterygomaxillary fossa, infratemporal fossa, temporal fossa, sinuses, and middle fossa by pushing the tumor medially with packing. The middle fossa can also be approached through the incision (Fig. 75-5). Most angiofibroma are *not* intracranial; rather, they are pericranial, having destroyed the bony floor of the middle cranial fossa. The tumor can be carefully removed from the middle cranial fossa, dura, and the cavernous sinus (Jones et al, 1986). Ideally, all the lobulations of the tumor should be extracted and should be seen to communicate with each other and with the body of the tumor (Biller, 1978; Boles and Dedo, 1976; Bremer et al, 1986; Jafek et al, 1973; Neel et al, 1973). All intervening bone that interferes with the removal of the tumor should be removed. Most large angiofibromas extend beneath the adenoid pad on the side of the lesion. Once the tumor is firmly grasped with a strong forceps, it is necessary to work with an elevator or index finger around the base of the tumor to aid in avulsion of the tumor.

Upon removal of the tumor, a search is made for any residual fingers, lobules, or pseudopods remaining in the body of the sphenoid bone. The cavity is packed; the packing is removed 5 to 7 days later with the patient under general anesthesia. Tracheotomy tube and feeding tubes are unnecessary. Postoperatively, patients have healed well and cosmesis has been satisactory, even for patients in whom the incision is used for reoperation.

Intracranial extension and residual tumor

Intracranial extension has been reported in approximately 20% to 25% of cases (Bremer et al, 1986; Jafek et al, 1979; Jones et al, 1986; Krekorian and Kato, 1977; Standefer et al, 1983). Intracranial extension is a result of anatomic proximity and not of a more aggressive tumor. As a general principle, the surgeon can carry out adequate extracranial resection by way of the lateral rhinotomy and its extensions and treat any residual tumor expectantly. Recurrence is treated only when symptoms justify the added risk (Bremer et al, 1986; Jones et al, 1986).

The tumor takes two major routes into the cranium (Neel et al, 1973). It can enter the cranial cavity by either or both of the two routes: by way of the middle fossa anterior to the foramen lacerum and lateral to the cavernous sinus and carotid artery, or through the sella medial to the carotid artery and lateral to the pituitary gland. The latter form of intracranial extension is difficult and hazardous to remove; it occurs in a very small number of patients. Often these tumors are intimately associated with the branches of the internal carotid artery and the cavernous sinus within the cranium and are difficult to manage surgically. This very small group of patients with central tumor extension into the cranium probably should be treated either with a combination of operation and radiation, or with external radiation only, whereas tumors may be safely removed from the middle fossa and may be considered pericranial.

At operation, the posterior wall of the maxillary sinus is carefully removed, and the tumor often can be found in the pterygomaxillary fossa. The tumor may destroy the root of

the pterygoid process of the sphenoid bone posteriorly. Large tumors extend into the infratemporal fossa through the pterygomaxillary fissure, where they expand and induce the classic facial fullness and actual bulging of the cheek. More enlargement leads to extension into the lower part of the temporal fossa, which results in swelling above the zygoma. When this occurs, the tumor usually extends into the infraorbital fissue; the inferior orbital fissure opens into the upper anterior part of the pterygomaxillary fossa and is an entrance into the lower end of the superior orbital fissure, which meets the inferior (lateral) orbital fissure, which meets the inferior (lateral) orbital fissure in the posterosuperior wall of the pterygomaxillary fossa. At this point, the tumor may destroy the greater wing of the sphenoid bone, forming the characteristic widening along the lower lateral margin of the superior orbital fissure and producing proptosis. If the tumor enlarges in the infratemporal and pterygomaxillary fossae, it can destroy the bone that forms the base of the pterygoid process where the body and the great wing of the sphenoid bone meet; the tumor then rests against the dura of the middle fossa, anterior to the foramen lacerum but lateral to the cavernous sinus.

The mean volume of blood replacement in the Mayo Clinic series was 1400 mL (range: 0-4000 mL) (Bremer et al, 1986). Hypotensive anesthesia did not reduce the volume of blood transfusion.

Some authors have relied on intraarterial embolization as a technique to decrease the vascularity of the tumors (Roberson et al, 1972; Sessions and Humphreys, 1984). Embolization has been used at the Mayo Clinic for the management of angiofibromas on a limited basis, usually in patients who have epistaxis at some time after surgical resection and in whom no gross tumor is obvious at the time of reexploration but a tumor blush is noted at angiography. Waldman et al (1981) used preoperative embolization routinely. Biller (1978) limited the use of embolization to large tumors that had an arterial blood supply from the internal and external carotid arteries or to tumors with intracranial extension that were thought to be resectable. McCombe et al (1990) found that the strongest predictor of recurrence was preoperative embolization. There was no greater predominance of large tumors in the embolized subgroup. They postulated that embolization shrinks the tumor but makes identification of tumor extensions more difficult so that the incidence of residual tumor is greater. As a corollary, they added that magnetic resonance imaging has made angiography "redundant" as a diagnostic and therapeutic method and has eliminated the morbidity of angiography and expoure to radiation.

An outstanding exception to primary surgical treatment is the series of patients from the Princess Margaret Hospital in Toronto, in whom external radiation was advocated as the primary method of treatment in most instances (Briant et al, 1978; Cummings, 1980a, 1980b, 1983; Fitzpatrick et al, 1980). The use of radiation as primary treatment is of much concern, especially in young patients, because thyroid carcinomas and radiation-induced sarcomas of bone and soft tissue are small but definite risks after radiation (Cummings, 1980b; Waldman et al, 1981; Witt et al, 1983). Also, lifelong follow-up may be necessary. The radiation induces more profound local changes such as atrophic rhinitis and occasionally osteomyelitis or soft-tissue necrosis. Radiotherapy may affect growth centers in the face, particularly in male adolescents at a time when rapid growth is occurring (Chandler et al, 1984; Neel et al, 1973). Goepfert et al (1982) have suggested that chemotherapy may be of some value in selected patients.

Outcome

Of the 30 patients in the Mayo series from 1972 to 1983, 29 had lateral rhinotomies and 1 had a small tumor removed by the transpalatal route (Bremer et al, 1986). The overall recurrence rate in this series was 17%: 5% (1 of 22) of the patients with extracranial tumors had recurrences, and 50% (4 of 8) of the patients with intracranial involvement had recurrences (Tables 75-3 and 75-4). The surgeon believed that the tumor was completely removed in 28 cases. Two patients had preoperative angiography, and one of them had preoperative embolization. Both patients had evidence of intracranial extension (stage III disease), and the embolization was by way of the internal maxillary artery and was performed one day before operation.

Seven patients required a secondary procedure: five for recurrent tumor and two for nasal lacrimal duct obstruction. Of the five patients with recurrent tumor, two had operation followed by embolization because of evidence of recurrent tumor and bleeding, one had embolization for recurrent tumor demonstrated by angiography, one had postoperative external radiation (3000 cGy) for recurrent tumor 3 years after operation, and one had recurrent tumor removed elsewhere 1 year after the initial operation. The two patients with nasolacrimal duct obstruction had dacryocystorhinostomies.

All 30 patients had long-term follow-up: 28 were alive without disease and 2 were alive with known residual disease but no symptoms. It is noteworthy that none of the patients have died of their disease. The natural history of this tumor, based on close follow-up after resection, indicates that regression of small residual tumors can occur. Several patients in this series and in a previous series with known residual tumor have not required treatment and have not had significant symptoms or signs of recurrence (Bremer et al, 1986; Neel et al, 1973). It is interesting that there is no clear relationship between the age of the patient and the outcome. Hemorrhage, nasal obstruction, and orbital encroachment are sometimes present with a primary tumor; however, many cases of residual tumor are asymptomatic. The surgeon should certainly attempt to remove the entire tumor, but incomplete resection is not life-threatening and can be treated expectantly. When symptoms develop, residual tumor can be managed successfully with appropriate secondary treatment (Jones et al, 1986).

In a review of treatment trends at the Mayo Clinic in 150 cases and after a careful review of the outcome, it was concluded that operation is the best primary form of treatment for virtually all patients, including most with intracranial extension (Bremer et al, 1986). The lateral rhinotomy approach and its variations, in one procedure, allow exposure of all the projections of the tumor. We have been unable to show that intracranial extension justifies a craniotomy. The use of adjunctive procedures - hypotensive anesthesia and preoperative embolization - has increased even though we have no evidence that they reduce bleeding or improve our capability to remove the tumor in its entirety. Hormones, cryotherapy, or external carotid artery ligation do not seem to be of value in the control of the tumor or hemorrhage at operation. In our surgical series the trend was toward more complete removal at the time of operation and fewer recurrences postoperatively. Mortality declined from 9% in the previous surgical series (Neel et al, 1973) to 0% in the most recent series (Bremer et al, 1986).

Malignant Neoplasms

Patients with malignant tumors of the nasopharynx have a bewildering array of signs and symptoms. Sometimes the nasopharynx is difficult to examine, even by physicians experienced in diagnosis and examination of this region. Scanlon et al (1958) described the consequences:

"Always a challenging problem, both from the diagnostic and therapeutic standpoint, malignant lesions of the nasopharynx are perhaps the most commonly misdiagnosed, most poorly understood, and most pessimistically regarded of all tumors of the upper part of the respiratory tract."

This statement is still true.

In addition to the clinical challenge, there are other matters of interest on which worldwide attention has been focused: the wealth of biologic, biochemical, and immunologic evidence that supports both an association between the Epstein-Barr virus (EB virus) and certain forms of nasopharyngeal carcinoma, and the fact that genetic, environmental, and viral factors all seem to play a part in the genesis of certain histologic types of nasopharyngeal carcinoma (Ablashi et al, 1983; Epstein and Achong, 1977; Henle and Henle, 1976, 1978; Henle et al, 1970, 1977; Klein, 1973; Lanier et al, 1981; Mathew et al, 1980; Neel and Taylor, 1989, 1990; Neel et al, 1980, 1983, 1984, 1985; Pearson et al, 1983).

Nasopharyngeal carcinoma

Until recent years there has been little agreement in the world literature about correct and acceptable pathologic classification of tumors of the nasopharynx. In the tumor registry of the Mayo Clinic, malignant tumors of the nasopharynx have been subdivided by light microscopy into three main groups: squamous cell carcinomas (keratinizing, nonkeratinizing, and undifferentiated); lymphomas; and a miscellaneous group consisting of adenocarcinomas, plasma cell myelomas, cylindromas, rhabdomyosarcomas, melanomas, fibrosarcomas, carcinosarcomas, and unclassified spindling malignant neoplasms (Table 75-5). The nonglandular, nonlymphomatous epithelial malignancies, collectively called *nasopharyngeal carcinomas (NPCs),* are the most common neoplasms of the nasopharynx.

Various epithelia - including keratinized and nonkeratinized squamous, pseudostratified, ciliated, and columnar - are found in the nasopharynx along with lymphoid tissue and glandular tissue. Therefore various benign and malignant tumors can arise from the minor salivary glands, lymphoid tissue, and connective tissue in the nasopharyngeal region. These are excluded from the epithelial tumors by definition, but the epithelial tumors show different degrees of differentiation and morphology.

Epidemiology

NPC is a relatively rare neoplasm in most parts of the world; in North America it makes up about 0.25% of all cancers. However, it accounts for approximately 18% of all malignant cancers among the Chinese. The incidence is even higher among southern Chinese of Kwantung province, the northern provinces, and Taiwan. Hsu et al (1982) have estimated

from surgical specimens in Taiwan that NPC is the most common cancer in males and the third most common cancer in females.

For populations in which Chinese genes have been introduced, the incidence of NPC rises. The marker for genetic susceptibility to NPC among Chinese has been suggested to be at the HLA-A2 histocompatibility locus. Even after migration, the Chinese have a higher frequency of NPC than other populations. Emigration from high-incidence to low-incidence areas - the USA and Canada, for example - reduces the incidence of NPC in the first generation, but it still remains well above that of white populations. Dickson (1981), in a unique, racially balanced series of 209 NPC cases in British Columbia, found that the incidence of NPC among Chinese born in China was 118 times the rate in whites and that in Chinese born in North America it was 7 times the rate in whites. The biologic behavior of the disease appeared to be the same in Chinese and non-Chinese individuals. Other factors implicates as causes of this include the EB virus, polycyclic hydrocarbons, nitrosamines from dry salted fish, chronic nasal sinus infection, and poor hygiene.

Histopathology

Using light microscopy, pathologists can consistently divide NPC into three types based on the *predominant* histologic type in the primary lesion. These are the basis of a broad classification established by the World Health Organization (WHO) that is fairly well accepted by pathologists around the world: squamous cell carcinoma (WHO type 1, Fig. 75-6); nonkeratinizing carcinoma - that is, transitional cell carcinomas (WHO type 2, Fig. 75-7); and undifferentiated carcinomas - lymphoepitheliomas and anaplastic carcinomas (WHO type 3, Fig. 75-8) (Batsakis et al, 1981; Shanmugaratnam, 1978; Weiland, 1978). Electron microscopy shows ultrastructural characteristics (desmosomes, tonofibrils) of squamous (epidermoid) carcinomas in the entire spectrum of these tumors, which at one extreme are well-differentiated and keratinizing types and at the other extreme are undifferentiated and anaplastic variants.

The WHO type 1 carcinomas show distinct intercellular bridges and abundant keratin production. Various degrees of these differentiating features can be observed. The tumor is similar microscopically to other squamous carcinomas of the upper aerodigestive tract and does not appear to be unique to the nasopharynx. About 25% of the tumors in North American patients all into this category (Neel et al, 1984). The WHO type 2 and type 3 tumors have a greater degree of tumor pleomorphism than the keratinizing type of tumors. There may be any of several microscopic patterns - spindle cell, transitional cell, lymphoepithelioma, clear cell, anaplastic, and others; combinations of these patterns are fairly common. These combinations, in conjunction with the ultrastructural features common to all WHO type 2 and type 3 tumors, are the reason why these tumors are considered to be variants of nonkeratinizing NPC rather than as distinct tumor entities. Indeed, a substantial body of clinical and serologic evidence supports the theory that carcinomas of the nasopharynx can be classified as *two distinct disease:* namely, squamous cell carcinomas (WHO type 1) and a combined group of nonkeratinizing and undifferentiated carcinomas (WHO types 2 and 3) (Neel et al, 1980, 1983, 1984, 1989; Pearson et al, 1983).

Other classifications have been complicated and impractical and have failred to acknowledge the heterogeneity within the nonkeratinizing and undifferentiated groups.

Nevertheless, both groups appear to be unique to the nasopharynx or, at most, to the lymphoepithelial tissues of Waldeyer's ring. The criteria for these categories have been reviewed in detail (Shamugaratnam, 1978; Weiland, 1978).

Clinical findings

The complaints of patients with NPC are related to the location of the primary tumor and the degree of spread. Generally, there are subtle symptoms and signs that are confusing to primary care physicians, otorhinolaryngologists, neurologists, ophthalmologists, and other specialists until the disease has reached advanced stages. Late diagnosis accounts for the poor outcome in many cases.

Hearing loss and a lump in the neck are the most common reasons for seeking medical attention (Dickson, 1981; Neel et al, 1983; Prasad, 1979; Scanlon, 1967). A tumor in the lateral nasopharyngeal wall, near or directly involving the mucosa of the eustachian tube orifice or, particularly, Rosenmüller's fossa, leads to tubal malfunction, a sensation of ear blockage, serous otitis media, and conductive hearing loss. Because the surface epithelium of the nasopharynx is endowed richly with lymphatics that communicate freely across the midline, bilateral metastasis to the lymph nodes is common. Nodes high in the neck and ipsilateral to the primary cancer, however, are usually affected first. Therefore patients with a primary carcinoma in the nasopharynx often are first seen for evaluation of a lump in the neck; a primary cancer in the upper airway and food passages should be sought before any surgical procedure (such as a biopsy) is undertaken in the neck.

Large primary tumors of the nasopharynx obstruct the choana and nasal airway, sometimes causing blood-tinged anterior or postnasal drainage. Superior extension of tumor through the foramen lacerum, which is an unimpeded pathway near Rosenmüller's fossa into the cranium, leads to cranial nerve involvement (Applebaum et al, 1982; Hara, 1969). In such cases, radiographic evidence of bone destruction at the skull base often exists. Most commonly cranial nerve VI is the first to become involved: diplopia results from external rectus paresis, and the eye signs may be further complicated by involvement of cranial nerves III and IV. A characteristic pain high in the neck, facial pain, or facial paresthesia reflects tumor infiltration of cranial nerve V. Tumor in the proximity of the jugular foramen leads to paresis or paralysis of cranial nerves IX, X, and XI - the so-called jugular foramen syndrome; more widespread involvement of the skull base leads to involvement of cranial nerve XII. Classically, diagnosis of upward spread of the tumor has been based on the radiographic demonstration of invasion of the base of the middle fossa, usually in the region of the foramen lacerum, or on involvement of either the anterior group of cranial nerves (nerves I to VI, the so-called petrous sphenoid route) or the posterior group of cranial nerves (nerves VII to XII, along the base of the posterior fossa by way of the retroparotidean route). These pathways of spread have been described by Ackerman and del Regato (1970). Radiographic evidence of bone destruction or involvement of either of these two groups of cranial nerves may be considered evidence of superior invasion in most cases (Scanlon et al, 1967).

The incidence of distant metastasis at the time of diagnosis in North American patients is less than 3%, but in other parts of the world, metastasis at the time of diagnosis is much more common.

The symptoms and signs of NPC and their frequency at diagnosis are shown in Fig. 75-9).

Diagnostic evaluation

Clinical. The diagnosis of NPC is made during the course of a head and neck examination, which must include indirect (mirror) nasopharyngoscopy. This office examination may be supplemented with endoscopic nasopharyngoscopy. Computed tomographic scans of the head and, specifically, of the skull base and nasopharynx should be obtained and studied. Invasion of the base of the skull is seen in approximately 25% of cases (Neel and Taylor, 1983). Most physicians advise computed tomographic scanning of the nasopharynx and head, with and without contrast medium, not only as part of the evaluation but also for treatment planning (Wang, 1983). It is important to look for intracranial extension too; in this case, magnetic resonance imaging will help delineate intracranial extensions.

To substantiate the diagnosis, a specimen of tissue should be removed from the tumor, either in the operating room with the patient under general anesthesia, or in the office, and studied by histopathologic examination and by EB virus-serologic testing.

Immunologic. Detailed immunologic and biochemical investigations have provided evidence that EB virus is associated etiologically with certain forms of NPC in both high- and low-incidence areas of the world. In addition, these investigations have identified certain biologic characteristics of this virus that have clinical importance, both in the diagnosis of NPC or suspected (occult) NPC and in the clinical management of the patients. The importance of viral markers has been the subject of intense worldwide study (Ablashi et al, 1983). Specific viral markers can be reliable aids in the diagnosis and clinical management of patients with NPC. Further investigation of these viral phenomena may lead to development of screening programs in high-incidence areas, new therapeutic approaches, and specific methods of prevention.

Serum specimens are assayed by indirect immunofluorescence procedures for titers of IgG and IgA antibodies to viral capsid antigen (VCA) and to the diffuse component of early antigen (EA). The EA and VCA (IgA) tests are the most specific tests for diagnosis, and the VCA (IgA) test is the more specific of the two. In addition to these immunofluorescence studies, sera are titrated for antibody to the EB virus-induced membrane antigen complex with the antibody-dependent cellular cytotoxicity assay. This test appears to be highly predictive of the clinical course. Unfortunately, this test is not yet commercially available.

Positive antibody titers are obtained significantly more often in sera from patients with NPC than in sera from control populations. In an ongoing prospective collaborative study of NPC in 151 North American patients (Neel et al, 1983), 73% of the sera has been positive for anti-EA (IgG) antibodies and 68% for anti-VCA (IgA). The outcome was virtually identical at the completion of the study of 182 patients (Neel and Taylor, 1990). The comparisons with control groups are shown in Table 75-6. The control groups were closely similar in their serum characteristics; no large differences existed, and no group had consistently higher or lower titers than the others. Within the control groups, however, were patients with specific otolaryngologic disorders who had higher titers than their control group as a whole. The outstanding subpopulations in these control groups are patients with

squamous cell carcinomas of the ethmoid or tongue, patients with chronic lymphocytic leukemia, and patients with inflammatory nasal polyps (Neel and Taylor, 1990; Neel et al, 1984, 1985).

The relationship of the antibody titers to the histopathologic type of NPC is striking. Whereas the overall average of positive antibody titers (from each test and each WHO type; Table 75-7) was 68%, the titers were elevated consistently in cases of WHO type 2 and WHO type 3, averaging 85% positive. This differed significantly from the findings in cases of WHO type 1, in which only 35% were positive for anti-EA antibodies and 16% for anti-VCA (IgA), which is the more specific test. Also, the geometric means of antibody titers of the anti-EA were twofold and three fold higher in WHO types 2 and 3 sera, respectively, than in WHO type 1 sera.

In cases of occult and early NPC - stage 1, in groups staged by one or another of three systems - anti-EA titers were positive in 100%, and positive IgA anti-VCA titers ranged from 90% to 94% (Table 75-8). In all cases, the nasopharyngeal tumor was small and limited to a small area in the nasopharynx. The EA and VCA tests can complement the process of diagnosis and are especially useful in directing attention to the nasopharynx in patients with occult NPC (Neel et al, 1981a). They might be considered for screening programs in high-incidence areas of the world.

The antibody-dependent cellular cytotoxicity (ADCC) titers obtained at diagnosis often predict the clinical course of WHO types 2 and 3 NPC (Neel et al, 1983). Fig. 75-10 shows freedom from progression (clinically detectable metastatic disease) in a high-titer group and a low-titer group. The association between low titers and known progression was strongly significant at 3 years; with longer follow-up the association with death was strongly significant (Neel and Tayloy, 1989). This association, however, was found only in cases of WHO types 2 and 3 and not in well-differentiated WHO type 1. At diagnosis ADCC titers appear to identify individual patients who could be candidates for systemic therapy from the outset.

Most patients with the poorly differentiated types of NPC have IgA antibodies to EB virus antigens in their sera. Mathew et al (1980) found that IgA antibodies purified from the sera of patients with NPC blocked the ADCC reaction, which is mediated by IgG anti-EB virus antibodies directed against membrane antigens. Furthermore, an inverse relationship exists between specific IgA and ADCC antibody titers. Perhaps blocking of the IgG antibodies or by IgA antigen-antibody complexes is the reason that ADCC titers are low in cases of NPC. All of this also presumes that the ADCC reaction occurs in vivo - a supposition that may or may not be true but does not detract from the specificity of the test.

In Chinese populations, associations have been demonstrated between NPC and certain human leukocyte antigen (HLA) alleles: A2, Bw46, and B17. The associations with A2 and Bw46 appear to be additive. Bw46 is an extremely uncommon antigen among whites. In a study of HLA and NPC in whites, no significant associations were found (Moore et al, 1983). This finding may mean that no HLA allelic association with NPC exist in whites, or that HLA associations are weak and were not detected.

Clinical stagings systems

Traditional systems (TNM). Although no international agreement exists on a single "best" staging system, several are well known: the AJC (American Joint Committee for Cancer Staging, 1977), the UICC (Union Internationale Contre le Cancer, Harmer, 1978), and the Ho system (Ho, 1978a, b; Neel et al, 1981b).

The AJCC system as it is now called (American Joint Committee on Cancer) is used most commonly in the USA by institutions concerned with cancer and the reporting of results. Major criticism of this system relate to the description of the extent of the primary tumor and of the regional lymph nodes.

Determinations of the extent of NPC can be difficult, even for expert examiners and even when the nasopharynx is well visualized with mirrors or endoscopic instruments, because submucosal extension beneath a normal-appearing surface mucosa is common. Furthermore, the definition of "posterosuperior" and "lateral" walls is a problem. The posterior part of Rosenmüller's fossa is in part the meeting point of the lateral and posterior walls. Tumors often arise in this site, and attempts to designate their extent as TIS (in situ), T1, or T2 - as is done in the AJCC and UICC systems - are likely to be ambiguous. Indeed, no appreciable difference in survival exists in these subgroups (Neel and Taylor, 1989; Neel et al, 1985). The Ho system recognizes this. Of further concern is the fact that T4 refers to tumor invasion of the skull, cranial nerve involvement, or both. Also, stage IV embraces patients with M1, T4, N2 disease; no patient with M1 diseas survives 5 years, whereas some patients with T4 and N2 disease do survive. Therefore patients with M1 disease should be staged separately (as recommended by Ho).

Another point of controversy in the AJCC system is cervical node classification as it relates to level, involvement of one or both sides of the neck, nodal mobility, and size of the metastatic deposit or deposits. The AJCC and UICC classifications were designed primarily as guides for surgical treatment and not for radiotherapy. Both systems place more emphasis on whether the nodal involvement is unilateral or bilateral and on whether the nodes are mobile or not than on the level of the nodal involvement. These issues need clarification; it is hoped that within the next few years an internationally accepted classification system can be devised and adopted.

It appears that nodes low in the neck indicate a poor prognosis (Dickson, 1981; Ho, 1978a; Neel and Taylor, 1989; Neel et al, 1981b; Scanlon et al, 1967). In the study by Scanlon et al (1967), if the involved upper cervical nodes were mobile, their unilaterality or bilaterality did not seem to affect survival. But involvement of lower jugular nodes was more unfavorable, once again regardless of whether it was unilateral or bilateral. These data reflect well on Ho's system, in which involvement of nodes low in the neck is designated stage III and involvement of supraclavicular nodes is stage IV.

All things considered, it is Ho's system (1978a, b) among the traditional TNM systems that appears to give the best correlation of stages with survival.

Changes in technology and serologic testing may help refine all the staging systems. Originally, radiologic study of the skull base used only plain radiographs. Then tomograms

were added; currently, computed tomographic scanning of the head is the primary roentgenologic study. Undoubtedly the thoroughness of the radiologic investigation sometimes has a bearing on the clinical staging of a case. It also appears that serologic testing may play a useful role in the staging of NPC.

A new view of staging. Traditional cancer staging systems mainly describe and classify the extent of disease (TNM) and are not based on other characteristics or variables that could have an important bearing on treatment programs. We have formulated a combination of variables, including some of the traditional characteristics of extent of disease, that provides a more accurate prediction of prognosis using Cox refression methods (Neel and Taylor, 1989; Neel et al, 1985). These variables form the basis of the new staging system in terms of a prognosis score called *score to death* (Table 75-9). A simplified working formulation for staging by score is shown in Table 75-10 (Neel and Taylor, 1989). A second system that includes antibody-dependent cellular cytotoxicity titer - that is, score to death including the titer - was developed because a high titer correlated strongly with a good prognosis, although a commercial assay is not available.

The two new systems are better predictors of outcome than are the traditional staging systems.

Management

Management of NPC consists primarily of supervoltage irradiation. The primary neoplasm and the primary echelon of lymph nodes are included in large lateral opposed portals. It appears that encompassing this volume with fields that average 10 cm x 13 cm can induce local control in all cases of T1 and T2 disease (Hoppe et al, 1976). Small primary tumors may be sterilized with 6500 cGy given at rates of 175 to 200 cGy per day, but large tumors or tumors involving cranial nerves of the base of the skull requires doses of 7000 cGy or more, usually with smaller fields or electron beam supplements. As the radiation dose is increased, the incidence of complications increases significantly.

Prophylactic irradiation of the lower cervical and supraclavicular lymph nodes to 5000 cGy by direct anterior fields with similar fractionation has prevented the extension of tumor to lymph nodes in those regions.

Radical neck dissection is seldom necessary. This surgical procedure is reserved for the occasional case in which radiation therapy has controlled the primary tumor but has failed to control cervical metastasis. Operation of the skull base for recurrent or residual NPC after radiation failure at the primary site may be of value in a few carefully selected patients (Fee et al, 1988).

One must consider the finding that cervical node biopsies may reduce survival (Dickson, 1981). This underscores the desirability of a thorough otorhinolaryngologic examination. Establishing the diagnosis of NPC by examination of tissue from the nasopharynx and by serologic testing rather than by biopsy of the neck is safer and certainly advisable.

Intracavitary radioactive implants may supplement external irradiation to the nasopharynx as part of primary treatment, or they may be reserved for management of recurrent or residual tumors. Occasionally, cryotherapy is applied in the nasopharynx as treatment for recurrence. Although the use of chemotherapy is limited, it is sometimes helpful for palliation after radiation treatment fails. Even after a recurrent or residual tumor becomes apparent, life may continue for years, and patients may suffer intractable pain. In the future, irradiation and immunotherapy in combination may yield better results.

The remarkable immunologic associations of NPC encourage the belief that with better understanding of immunologic mechanisms, immunotherapy will become a treatment option for this disease in the near future (Neel and Huang, 1981). Optimism regarding this development is based in part on the premise that ADCC occurs in vivo; if in fact it does, then a high-titered serum containing IgG antibodies directed against EB virus membrane antigens may have a good effect on patients with circulating IgA "blocking" antibody. One could consider this therapeutic approach with plasmapheresis to remove a specific IgA-blocking antibody.

New therapeutic approaches are usually studied in patients with large recurrences, but as a general rule, immunotherapy and perhaps chemotherapy will most likely be beneficial in patients with minimal, clinically nonapparent residual disease.

Prevention

One of the most controversial issues in EB virus-associated diseases is related to the development and use of vaccines (Ablashi et al, 1983). Already the major EB virus-specific membrane glycoprotein from infected cells has been purified and shown to induce neutralizing and cytotoxic antibodies. Someday it may be possible to study the efficacy of a vaccine in high-incidence areas of the world.

Outcome

By life-table analysis, survival of 182 contemporary patients with and without recurrence after conventional radiation therapy was 60% at 3 years and 50% at 5 years after diagnosis (Neel and Taylor, 1989). Of the patients with WHO type 1 tumors, 37% survived to 3 years and 10% to 5 years; of those with WHO types 2 and 3 tumors, 65% survived to 3 years and 52% to 5 years (Neel and Taylor, 1989; Neel et al, 1983). Thus a definite trend existed toward more deaths being caused by NPC in the WHO type 1 group than in the others. Of special interest is the fact that the unique WHO 2 and 3 morphologic forms of NPC appear to be chronic diseases because the risk of death does not level off with time (beyond 5 years) as it does with most other cancers.

Dickson (1981) found very similar results in another study on Chinese and white patients. In most studies, overall 5-year survival is in the range of 30% to 48%; among the survivors, attrition in the next 5 years is about 10% (Hsu et al, 1982; Scanlon et al, 1967). Most of the recurrences after 5 years are in cases of WHO types 2 and 3 disease. The outcome depends not only on the histopathology of the tumor but also on the type and technique of radiation therapy, the stage of the tumor, and the age of the patient. Patients at the extremes of age have poorer survival (Applebaum et al, 1982; Hsu et al, 1982; Neel et

al, 1980; Scanlon et al, 1967).

Many of the differences in survival in the various staging systems are significant, but every system shows a clear trend to poorer survival with higher stage of disease. As expected, comparison of the AJCC and UICC systems showed no difference in survival between the small stage I and stage II groups (Neel and Taylor, 1989; Neel et al, 1985).

Nasopharyngeal carcinoma as two distinct diseases

A large body of clinical evidence supports the theory that carcinomas of the nasopharynx constitute two distinct diseases. This division was recognized by Scanlon et al (1967), who classified the nasopharyngeal carcinomas into two groups: "keratinizing squamous cell carcinomas" and "combined grade 4 undifferentiated carcinomas" (which are lymphoepitheliomas, anaplastic carcinomas, and transitional cell carcinomas in the old terminology). These would currently be classified as WHO type 1 tumors and combined WHO types 2 and 3 tumors. The EB virus serologic findings can be added to the clinical indications that WHO type 1 tumors are biologically different from WHO types 2 and 3 tumors (see Table 75-7). With types 2 and 3, onset is at an earlier age (Fig. 75-11), disease-free periods after treatment are longer, survival after treatment is greater, and early and advanced neck metastasis is more common (Applebaum et al, 1982; Dickson, 1981; Neel and Taylor, 1983, 1990; Neel et al, 1983; Scanlon et al, 1967). In addition, primary WHO types 2 and 3 tumors in the nasopharynx are often small, submucosal, and difficult to detect; indeed, they may be clinically occult. The tumors appear to be more radiation-sensitive than the WHO type 1 carcinomas, which are more likely to recur or persist in the nasopharynx after treatment. WHO type 1 carcinomas are of the common type seen in other regions of the upper airway and food passages.

Serologic testing has been a useful diagnostic aid in many of the Mayo Clinic cases of NPC, particularly those in which the tumors were small and submucosal - either difficult to see or occult. For example, if a metastatic tumor is found in the neck but its primary site is occult, positive titers provide reason for detailed investigation of the nasopharynx, including a more thorough examination with the patient under anesthesia and obtaining random biopsy specimens (Fig. 75-12) (Neel et al, 1981a). This approach can spare the patient a neck node biopsy; Dickson (1981), after comparing two groups with NPC metastatic lesions in the neck (one group differing from the other only in that patients had undegone neck biopsy before radiation treatment), found poorer survival rates in the group that had undergone biopsy.