Esthesioneuroblastoma

18

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Contents

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Esthesioneuroblastoma, also often called olfactory neuroblastoma, is a rare tumor thought to arise from the olfactory neuroepithelium. It may occur at any age and accounts for 1–5% of intranasal tumors with an estimated incidence of 0.4/million population (Broich et al. 1997; Ferlito et al. 2003; Thompson 2009). No sex predisposition has been reported. Recent reports favor a unimodal age distribution with the majority of patients diagnosed in the fourth and fifth decades of life (Resto et al. 2000; Ferlito et al. 2003; Jethanamest et al. 2007), but previously an additional peak of incidence in the second decade has been claimed (Elkon et al. 1979).

In children esthesioneuroblastoma is rare with an estimated incidence of 0.1/100,000 children up to 15 years, but it is the most frequent cancer of the nasal cavity in this age group, representing 28% of cases registered in a series of 47 patients below 19 years with nasal cavity tumors in the SEER database from 1973 to 2002 (Benoit et al. 2008). Only single cases have been reported in young children below 10 years of age, the youngest reported case being as young as 2 years (Woerner et al. 1986; Perkkio et al. 1991; Bobele et al. 1994; Kumar et al. 2002; Eich et al. 2005; Jethanamest et al. 2007).

The clinical and histological diagnosis of esthesioneuroblastoma is confusing, and misdiagnosis has been reported in quite substantial parts of patients, where histology was reassessed according to current immunohistochemical criteria (Hirose et al. 1995; Resto et al. 2000; Cohen et al. 2002; Eich et al. 2005). Therefore, clinical features reported in the literature should be interpreted with cautiousness if not proved in recently reported series.

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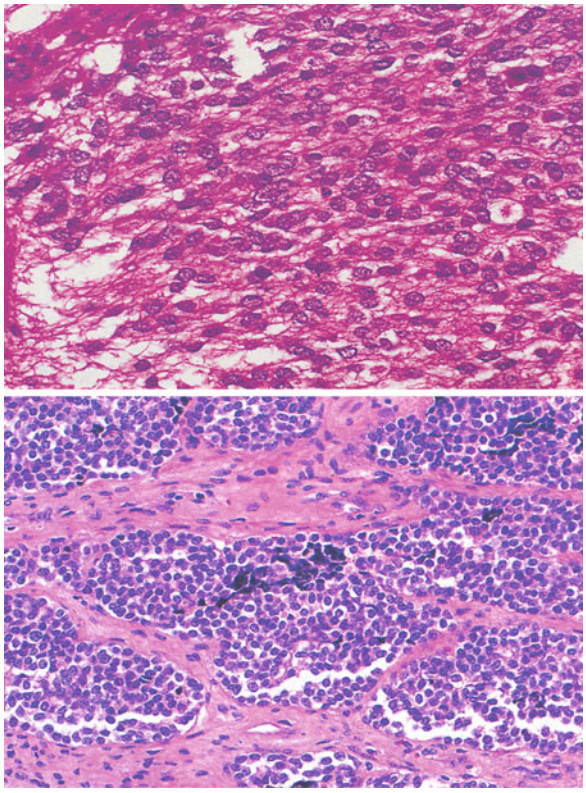

Fig. 18.1 Esthesioneuroblastoma, histology

18.1 Pathology

Esthesioneuroblastoma is a tumor with small, round, blue tumor cells arranged in a lobular architecture in neurofibrillary stroma (Fig. 18.1). Rosettes and pseudorosettes as well as calcifications may be found. Based on assessment of lobular tumor architecture, mitotic activity, nuclear pleomorphism, rosettes, and tumor necrosis, Hyams et al. proposed a grading system, which is correlated to prognosis (Hyams et al. 1988). Immunohistochemically, esthesioneuroblastoma may stain positive for synaptophysin, chromogranin, CD56, neuron-specific enolase, NFP, and S-100 protein, but negative for desmin, myogenin, leukocyte common antigen, and CD99 (reviewed in Faragalla and Weinreb 2009; Thompson 2009).

Due to the rareness of the disease, histological evaluation by a second experienced pathologist should be aimed for. Other small round cell tumors as rhabdomyosarcoma, tumors of the Ewing tumor family, neuroblastoma, lymphoma, and, less common in childhood, neuroendocrine carcinoma, squamous cell carcinoma, and sinonasal undifferentiated carcinoma, have to be ruled out. Although previously controversially discussed (Sorensen et al. 1996), it has meanwhile been shown that esthesioneuroblastoma does not belong to the Ewing tumor family, as CD99/MIC staining and the typical translocations are lacking (Nelson et al. 1995; Argani et al. 1998; Mezzelani et al. 1999). From the histopathological point of view, metastatic neuroblastoma would present with identical findings as esthesioneuroblastoma. Amplification of the MYCN oncogen, which is found in many aggressive neuroblastomas, has so far not been reported in esthesioneuroblastoma. Thus, in single cases, molecular assessment of the tumor specimen, showing Ewing tumor family typic translocations or MYCN amplification, may be helpful to rule out esthesioneuroblastoma.

18.2 Staging

The origin of esthesioneuroblastoma is confined to the olfactory mucosa involving the superior turbinate, cribriform plate, and the superior one third of the nasal cavity. It may spread into the paranasal sinuses, the orbits, and – through the lamina cribriformis – into the cranial cavity. Although dystopic sites of origin in the nasopharynx, in the maxillary sinuses, and intracranially have been reported (Seccia et al. 2010; Banerjee et al. 1992; Jugie et al. 1992; Sharma et al. 2002; Mariani et al. 2004; Wormald et al. 2011), a diagnosis of esthesioneuroblastoma outside the nasal cavity should only be made with great cautiousness (Mills 2002).

Symptoms are related to the site of origin and the local invasion and may present as long as several months prior to definite diagnosis (Dulguerov and Calcaterra 1992). Unilateral nasal obstruction, recurrent epistaxis, and – less common – anosmia are observed as well as ophthalmic manifestations like periorbital pain, excessive tearing, visual disturbance, or ptosis (Rakes et al. 1985). Occasionally headache, nerve palsies due to involvement of cranial nerves, or hormone excess syndromes such as Cushing syndrome or inappropriate antidiuretic hormone secretion have been reported (Osterman et al. 1986; Arnesen et al. 1994; Myers et al. 1994).

Table 18.1 Esthesioneuroblastoma: (modified) Kadish staging system and prognosis

Stage		Stage distribution	Disease-specific survival rates (at 10 years)	Stage distribution	Proposed therapy in children
		As reported in (Jethanamest et al. 2007) based on registry data, $n=261$, all ages		As reported in (Broich et al. 1997) based on systematic literature review, $n=553$, all ages	
A	Tumor confined to the nasal cavity	17.2%	90%	18.3%	Resection
B	Tumors involving the nasal cavity and extending into the paranasal sinuses	49.8%	68.3%	32.3%	Resection + radiotherapy
C	Tumor extending beyond the nasal cavity and paranasal sinuses (includes involvement of orbit, base of skull, intracranial cavity)	3.8%	66.7%	49.4%	Resection + radiotherapy ± (neoadjuvant) chemotherapy
D	Any tumor with distant sites	29.1%	35.6%		

In 1976, Kadish et al. (1976) proposed a staging system based on the pattern of spread (Table 18.1). Kadish A tumors are confined to the nasal cavity, while Kadish B tumors infiltrate the paranasal cavities. Kadish C tumors extend beyond the nasal and paranasal cavities (Kadish et al. 1976). Later, the system has been modified by adding the category Kadish D for tumors with metastases. The Kadish system correlates to prognosis and is still in use, although other systems based on the TMN classification have been proposed (Biller et al. 1990; Dulguerov and Calcaterra 1992). Larger cohorts report about one third of the patients to present with Kadish stage C.

Distant metastases are thought to be very rare and to occur in less than 10% of patients. Metastases to lung, CNS, bone, liver, and bone marrow have been reported (Franklin et al. 1987; Koka et al. 1998; Chao et al. 2001; Argiris et al. 2003; Bradley et al. 2003; Eich et al. 2003; Bachar et al. 2008). It is assumed that, due to the difficult diagnosis, parts of those reports include misdiagnosed tumors and that the real proportion of esthesioneuroblastoma with distant metastases is even lower, as reflected in more recent published series (Diaz et al. 2005). However, locoregional spread to cervical lymph nodes seems to be encountered more often. Approximately 5–10% of all patients present with evidence of disease in the neck, while cervical lymph node involvement in the course of the disease will be found up to a quarter of patients (Dulguerov et al. 2001; Rinaldo et al. 2002; Bachar et al. 2008; Gore and Zanation 2009; Ozsahin et al. 2010).

Investigations at initial work-up include CT scan which usually shows a homogenously enhancing lesion, with bone erosion, invasion of the adjacent structures, and often with calcifications. MRI images help to delineate the extent of the disease, which appear isointense or hypointense to brain on T1-weighted images and hyperintense on T2-weighted images with marked enhancement after gadolinium (reviewed in Thompson 2009) (Fig. 18.2).

Besides the imaging of the primary tumor site and the neck, the initial work-up should include the search for distant metastases in CNS, lung, liver, bone, and bone marrow. In bone marrow, multiple sites should be assessed as the diagnosis of neuroblastoma or rhabdomyosarcoma should be considered. Somatostatin receptor imaging and FDG-PET have been reported to give positive results in patients with esthesioneuroblastoma and might be helpful in assessing the extent of the disease at diagnosis and during treatment (Ramsay et al. 1996; Freeman et al. 2005; Nguyen et al. 2006; Rostomily et al. 2006). Only a single patient with esthesioneuroblastoma has been reported to show positive mIBG uptake (Kairemo et al. 1998), but mIBG scintigraphy might be helpful in those cases where a metastatic lesion of a neuroblastoma is discussed. However, these imaging techniques have not been systematically addressed in larger cohorts of patients with esthesioneuroblastoma so far.

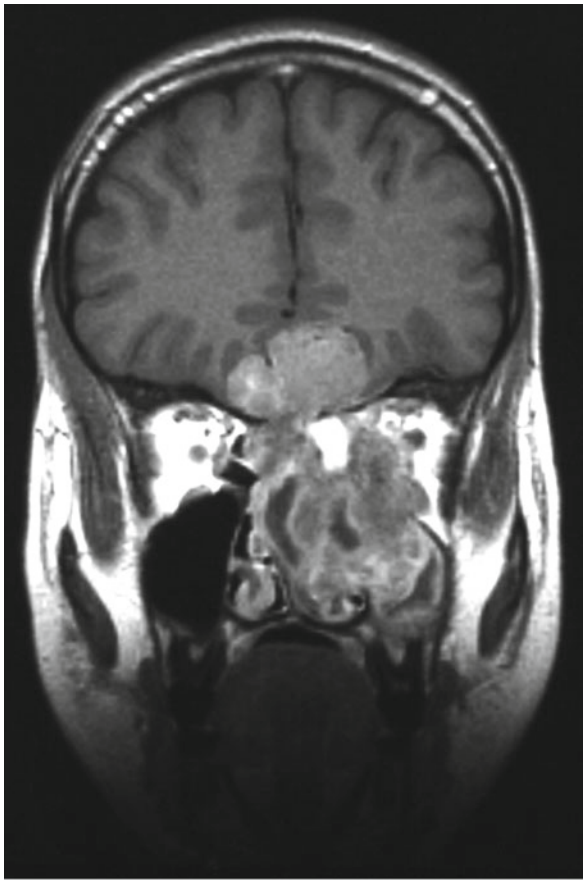

Fig. 18.2 Esthesioneuroblastoma, Kadish stage C, infiltrating the orbita, the nasal and paranasal cavities, and, through the lamina cribriformis, the brain (MRI)

18.3 Prognosis and Therapy

Due to the rareness of the disease, literature on prognosis is not reflected on large, homogenously treated cohorts. Nevertheless, it seems quite clear that grading, staging, the presence of metastases, and the treatment received influence prognosis. Kadish et al. reported patients with advanced stage (Kadish stage C) to be younger at diagnosis (median age 30.4 years) (Kadish et al. 1976). Vice versa, older age at diagnosis was correlated with better outcome in one series (<61 vs. >61 years) (Ozsahin et al. 2010), but this was not confirmed by others (<20 vs. >20 years (Eich et al. 2003); <50 vs. >50 years (Dulguerov and Calcaterra 1992)). In childhood, a high incidence of advanced stages is discussed (Lochrin 1989; Kumar et al. 2002), leading to the assumption that esthesioneuroblastoma in childhood shows an aggressive behavior; however this has never been proven in larger comparative studies.

To some extent, the amount of therapy needed is discussed controversially in the literature. Table 18.1 sets our proposal for the treatment in children in relation to the survival estimates as reported from a large cohort of 261 patients with esthesioneuroblastoma (Jethanamest et al. 2007).

Complete resection of the primary has been correlated to prognosis and is considered the backbone of all treatment strategies (Goldsweig and Sundaresan 1990; Devaiah and Andreoli 2009). Planning of the surgery may involve different subdisciplines (head and neck surgeons, neurosurgeons, ophthalmologists). Although most often open surgeries have been performed, endoscopic resections seem not to be inferior, as long as oncologic principles with clearance of margins are maintained (Lund et al. 2010; Snyderman et al. 2008; Folbe et al. 2009). To gain resectability in locally extended tumors, preoperative chemotherapy or radiotherapy proved efficient (Foote et al. 1993; Eich et al. 2003; Eich et al. 2005).

Kadish stage A tumors, especially when presenting with low-grade histology, seem to be sufficiently treated by surgery alone (with or without radiotherapy), but account only for a minor part of patients. In higher stages, the addition of radiotherapy with doses ranging from 55 to 65 Gy is claimed (Foote et al. 1993; Chao et al. 2001; Dulguerov et al. 2001; Eich et al. 2001). The planning of the radiotherapy may be hampered by adjacent endangered structures as eye and CNS and may require modern radiation techniques as intensity-modulated radiotherapy, proton irradiation, or stereotactic radiosurgery (Bhattacharyya et al. 1997; Walch et al. 2000; Zabel et al. 2002a, b; Tselis et al. 2008; Sterzing et al. 2009).

Although some authors abrogate the positive influence of chemotherapy, most authors support the need for a multimodal treatment strategy including surgery, radiotherapy, and chemotherapy in tumors of Kadish stage C (with or without metastases), however, without reaching a consensus on kind and amount of chemotherapy needed (Goldsweig and Sundaresan 1990; McElroy et al. 1998; Oskouian et al. 2002; Eich et al. 2003, 2005; Loy et al. 2006; McLean et al. 2007; Kiyota et al. 2008; Nichols et al. 2008; Porter et al. 2008). In children, chemotherapy regimen of soft tissue sarcoma or neuroblastoma protocols have often

been used; in adults, treatment with platinum-based regimens and others have been reported.

If cervical lymph nodes are involved, neck dissection and postoperative radiation therapy are discussed (Zanation et al. 2010), while cervical treatment seems not required in N0 patients. However, to discover late-evolving lymph nodes, adequate imaging of the neck should always be included in the follow-up of the patients (Gore and Zanation 2009).

Relapses and metastases usually develop within the first 2–3 years after diagnosis, but late relapses more than 5 years after therapy have been reported (Morita et al. 1993; Eden et al. 1994; Loy et al. 2006), indicating the need for a long follow-up, which, in a childhood population, should always include the care for therapy-related sequelae. The need for local control including expanded surgical procedures and high-dose radiotherapy poses specific problems in the pediatric age. Long-term sequelae in children include damage to craniofacial growth and permanent dentition, endocrine dysfunctions, and loss of sense of smell.

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