Ewing’s sarcoma (ES) is the second most common malignant bone tumor. It affects long bones in 47% of cases, flat pelvic bones — 29%, ribs and vertebrae — 12%, the mandibular bone and skull — 9% of cases [1, 12].

ES was first described by an American oncologist J. Ewing in 1921 as a “diffuse hemangioendothelioma of bone”. Since that time, a number of researchers have attempted at elucidating the real histogenesis of this tumor. Morphological, immunohistochemistry, and electron microscopy data show that this neoplasm is a “primitive mesenchymal tumor with multipoten differentiation” [17].

This phenomenon has been verified by studies based on cell lines and tissue sections [14–16]. A tumor with a similar histological presentation, immunohistochemistry and molecular genetic parameters was also described for soft tissues [20]. In combination with other current studies [specific translocations t(11;22) and t(21;22)], this gave grounds for using the term “Ewing sarcoma family of tumors” in literature more frequently [1, 3].

The highest incidence rate of bone ES is observed among 5–13-year-old patients. In 75% of cases, these tumors affect people younger than 20 years of age. ES constitutes 6–9% of all malignant bone tumors among children. There is a certain predominance of male patients; the male : female ratio is 1.6:1 [4, 12].

ES is characterized by an appreciably aggressive course. It has multicentric manifestation in 30% of cases, while there are distant metastases as early as a primary focus is detected in 14–45% of cases [5, 12].

Histopathologic parameters of ES include monotonous layers of cytoplasm-depleted monomorphic round-ed cells, round nuclei, and small nucleolae. The presence of PAS (periodic acid-Shiff staining)-positive grains in the cytoplasm of tumor cells is a typical pathomorphological feature; it indicates the glycogen is present and makes ES differ from other similar tumors, such as lymphoma and rhabdomyosarcoma. Molecular genetic analysis detects pathognomonic chromosomal translocations t(11;22)(q24;q12). Immunochemical expression of CD99 and transmembrane protein encoded by the MIC-2 gene are the additional data that verify the diagnosis [9–12]. Both primary and metastatic ES can affect the skull base.

A comparative analysis of the primary and metastatic ES of the skull base in patients operated on in the same hospital was carried out.

Materials and Methods

9 patients with ES of the skull base were operated on in the Burdenko Neurosurgical Institute over the period between 2003 and 2011. The tumor was primary in 5 cases, while being of metastatic origin in 4 cases.

As compared to the metastatic ES of the skull base, primary ES affects younger patients. In 3 patients, primary ES of the skull base was identified at the age below 3 years; the age of two other patients when diagnosed with primary ES was 16 and 58 years (Table 1).
Patients with skull-base metastases aged 13—20. The primary tumors developed in them at the age from 11 to 14 years. The period between the time when a primary tumor was detected and skull-base metastasis manifested itself varied from 24 months to 8 years.

Male patients predominated in our group. The male : female ratio was 5:4 (1.25:1).

Medical history plays the key role in differential diagnosis of the primary and metastatic ES. In all the cases of metastatic lesion of the skull base, the past medical history comprised the data on the primary tumor and previous therapy for the primary focus.

Localization of the tumor of the skull base was determined according to the CT and MRI data. Both CT and MRI were performed in 3 patients. Osteolytic changes in the form of destruction of bone structures yielding defects with irregular contours and small bone inclusions in tumors were seen in the CT scans in all patients (Fig. 1). However, the CT data are insufficient to perform a thorough diagnostics and determine the therapy strategy. Hence, all patients with ES of the skull base underwent an MRI of the brain with intravenous contrast.

According to the MRI data, the tumors mostly had heterogeneous polynodular structure, contained cysts, necrotic and hemorrhagic foci. The tumor tissue is hyperintense compared to normal brain and hypointense compared to liquor on T1 MRI. In case of MRI with intravenous contrast, tumor intensely and inhomogeneously accumulates the contrast agent (Fig. 2).

The CT and MRI data in patients with primary ES are virtually identical to those in patients with metastatic tumors. In the latter case, necrotic foci and cystic transformations are frequently detected.

Among the skull base structures, the petrous temporal and cuneiform bones were most commonly affected both in patients with primary ES and in those with metastases (Table 2).

In this group of patients with 4 cases of metastases, the tumor affected the basilar and bones in 2 and 2 cases, respectively.

<table>
<thead>
<tr>
<th>Table 1. Age distribution of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>1—5</td>
</tr>
<tr>
<td>6—10</td>
</tr>
<tr>
<td>11—15</td>
</tr>
<tr>
<td>16—20</td>
</tr>
<tr>
<td>Older than 20</td>
</tr>
</tbody>
</table>

In this group of patients with 4 cases of metastases, the tumor affected the basilar and bones in 2 and 2 cases, respectively.

Among the primary tumors, the tumor originated from the petrous temporal bone in two cases and from the occipital bone (while propagating to the areas of the occipital condyle and the jugular foramen) in one case. The basilar bone was affected in one case. In one patient, the tumor affected the frontal, temporal, and cuneiform bones.

The clinical presentation is caused by localization and the area to which the tumor has spread, while being independent of the fact whether it is primary or secondary. While the cases of calvarial lesions accompanied by headache and increased intracranial pressure have been predominantly reported in literature, the lesion of the skull base is primarily associated with the symptoms of cranial nerve lesions.

The general brain lesion symptoms (headache, nausea, and vomiting) were observed in 2 cases (Table 3). The general brain lesion symptoms in the form of sleepiness, adynamicity, and upward gaze paresis were observed in a 3-year-old child with a widespread tumor of the skull base and extensive effect on the brain, which resulted in edema and dislocation with compression of the 4th ventricle.

<table>
<thead>
<tr>
<th>Table 2. Occurrence of the tumor of the skull base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor localization</td>
</tr>
<tr>
<td>Petrous temporal bone</td>
</tr>
<tr>
<td>Cuneiform bone</td>
</tr>
<tr>
<td>Occipital bone</td>
</tr>
<tr>
<td>Several bones</td>
</tr>
</tbody>
</table>

Fig. 1. CT presentation of ES of the petrous temporal bone. Bone destruction and periosteal reaction are visualized.

Fig. 2. MRI scans with intravenous contrasting in patients with primary ES of the petrous temporal bone. Tumor has a solid and cystic structure, causes destruction of the petrous temporal bone, and nonhomogeneously accumulates the contrast agent.
servations were carried out for 11–34 months; in patients with primary tumors, for 18–92 months. We failed to follow up a 58-year-old patient with primary tumor of the petrous temporal bone after his discharge from the hospital. A relapse of metastatic tumor to the petrous temporal bone was observed in one patient 7 months after the metastasis was removed. The patient died 7 months after the reoperation because of generalization of the oncological process. Two patients with metastases to the basilar bone died of extracranial metastases three years after the metastasis had been removed. The patient with metastasis to the petrous temporal bone is followed up for 14 months without any signs of recurrence and extracranial generalization. No signs of recurrence are observed in the group of patients with primary ES of the skull base.

All the 9 ES cases were microscopically represented by a tumor consisting of small round cells of regular shape containing round or oval nuclei with the high nucleus–cytoplasm ratio separated by fibrous interlayers. Chromatin dispersion embedded in karyons imparts them the characteristic “mirror-like” appearance. The mitotic activity in ES cells was low in all patients. Well-pronounced necrosis of tumor tissue was detected in 2 patients with primary ES and 3 patients with secondary ES. The features of tumor morphology (almost in all patients) made it difficult to diagnose ES only according to the morphology; differential diagnostics with other small cell malignant cells (neuroblastoma, rhabdomyosarcoma, lymphoma, etc.) were required.

In all the cases, tumor cells expressed CD99 (p30/32MIC2) surface marker and vimentin on the membranes (Fig. 3). No expression of other markers (CD45, Desmin, Synaptophysin, Myogenin, Pan-Cytokeratin, etc.) was detected in tumor cells. A FISH analysis has revealed translocation between chromosomes 11 and 22 [t(11;22) (q24;q12)] in 90–95% of tumor cells, which is a pathognomonic sign of ES (Fig. 4).

Lesion of the basilar bone mostly resulted in ocular motility and facial sensitivity disorders. When the tumor localized within the petrous temporal bone, the clinical presentation mostly consisted of the symptoms of lesions of the facial and auditory nerves.

In one case, the lesion of the occipital bone and spreading of the tumor to the jugular foramen, occipital condyle, and the petrous temporal bone resulted in lesion of nerves IV, V, VII, IX, X, XII.

**Results**

Combined therapy including surgical evacuation of the tumor followed by chemo- and radiation therapy was used in all 9 cases. When performing surgical interventions, the surgeons sought to attain the maximum degree of tumor resection. While a neoplasm in patients with calvarial tumors can easily be totally removed, this procedure is almost infeasible in patients with tumors of the skull base because of the involvement of the functionally significant structures. The tumor was removed transcranially in 7 cases; subtotally and totally, in 3 and 4 cases.

The endoscopic transnasal approach to the tumors of the basilar bone was performed in two patients. In one of the patients, the surgical intervention was confined to biopsy and removal of the available tumor portion from the sphenoidal sinus. The main portion of the tumor localized in the medial regions of the mesocranial fossa, in the cavernous sinus. For this reason, a decision was made to abstain from removing it. Endoscopic subtotal removal of the tumor was performed in the other case.

RCT I and RCT II chemotherapy was performed in 3 and 5 patients, respectively. The number of courses varied from 8 to 10. In one case, the long-term outcome of a patient after he had been discharged from the hospital was not followed. In the remaining 8 cases, chemotherapy was followed by radiation therapy with the TBD varied from 30 to 50 Gy.

After the surgical intervention, 8 out of 9 patients were followed up during the period from 11 to 92 months. In patients with metastatic tumors, the catamnestic ob-

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>General brain lesion symptoms (headache, nausea, vomiting, optic disc edema)</td>
<td>2</td>
</tr>
<tr>
<td>Skull swelling</td>
<td>2</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>1</td>
</tr>
<tr>
<td>Ocular motility disorders</td>
<td>4</td>
</tr>
<tr>
<td>Visual loss (to complete blindness)</td>
<td>1</td>
</tr>
<tr>
<td>Occipital condyle syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Jugular foramen syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Facial and auditory nerves</td>
<td>4</td>
</tr>
<tr>
<td>Trigeminal nerve</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 3. Clinical presentation in patients with ES of the skull base**

Fig. 3. Immunohistochemistry study: tumor cells express the CD99 (p30/32MIC2) surface marker on the cells.
Discussion

ES occurs in patients younger than 20 years of age in 90% of cases; the highest incidence rate is observed in 5–13-year-old patients [8]. The number of reported ES cases in older patients is rather small. In a series of 14 observations described by K. Desai et al. [13], the youngest patient was 18 months of age, while the oldest one was 40 years old. The mean age of patients was 14.5 years; in most cases, the disease onset was recorded at the age younger than 30 years. A single case of ES of the skull base in a 54-year-old patient was reported in literature.

The disease prevailed in male patients. According to the published data [8], the male : female ratio is 1.6:1–1.8:1. In our observation series, the male : female ratio was 1.2:1.

Primary ES is more likely to affect long bone shafts (47%), pelvic bones (29%), ribs and vertebrae (12%). Skull lesions in patients with ES is observed in 6–9% of cases. The tumor is more likely to affect the frontal and parietal bones. Temporal squama and mastoid bone, ethmoid bone, eye socket, and petrous temporal bone are involved in the pathological process less frequently [1, 3, 7, 9].

Sporadic cases of skull base lesions (involving both the primary ES and its metastases) were reported. A total of 36 cases of primary ES of the cranium have been reported since the early XX century. Among them, the skull base lesion was reported in 13 (36.1%) of cases [13]. In this group, the lesions of the petrous temporal bone was observed in 6 cases; eye socket, in 4 cases; mastoid bone, in 2 cases; and ethmoid bone, in 1 case [13].

ES is prone to develop metastases. In 75–80% of cases, the metastases manifest themselves during the first two years after the primary tumor had been detected. They are more likely to affect lungs (57%) and bones (34%) [24, 28]. Metastases to the CNS develop in 10–37% of cases [5, 13]. A. Colak et al. [5] reported on 16% of cases of metastases to the CNS (most of the metastases had spinal localization). A. Kulick and J. Mones [15] reported on 32% of cases of CNS lesion and mentioned that cerebral manifestation is typically observed within the first 2 years in 90% of patients.

A comprehensive diagnostic strategy is used in patients with ES of the skull base. Past medical history plays the key role in differential diagnosis between the primary and metastatic ES [4]. In all the observations of metastatic lesions of the skull that have been reported, the medical history contained the data that the patient had had some organs affected with ES and had received treatment [5].

There are no pathognomonic X-ray signs that enable one to differentiate between the primary and metastatic ES [6]. Craniography and CT bone window photography of the skull revealed bone destruction [10]. Virtually no "onion skin" sign (which is roentgenologically typical of ES of long bones) has been observed in patients with skull lesion [10, 11].

According to the MRI data, tumors predominantly have a heterogeneous polynodal structure, contain multiple cysts, hemorrhagic and necrotic foci. The tissue shows hyperintensity with respect to brain and hypointensity with respect to the liquor in the T2-weighed image, while showing hypointensity with respect to brain and hyperintensity with respect to the liquor in the T1-weighed images. The tumor intensely accumulates the contrast agent when performing MRI with intravenous contrast [23].

The clinical presentation depends on localization and degree of tumor spread; its specificity remains the same regardless of the fact whether the tumor is primary or metastatic [5, 6]. According to the published data [11, 13], while headache (100%), increased intracranial pressure (75%), and skull swelling are the main symptoms in patients with convexital localization of the tumor, the clinical presentation mostly includes lesion of the cranial nerves in patients with tumor of the skull base. Lesion of the petrous temporal bone is characterized by facial nerve paralysis and hearing impairment. Tumor localization in the euneiform bone causes ocular motility disorders and disturbance of the trigeminal nerve. Lesion of the caudal nerves is observed rarely, when the tumor localizes in the posterior cranial fossa and affects the occipital condyle [24].

The exact diagnosis is arrived at according to the data obtained by pathomorphological examination verified by the results of immunohistochemistry and genetic testing [16].

The differential diagnostic procedure should be performed using intracranial tumors with round cells, such as primitive neuroectodermal tumor, rhabdomyosarcoma, metastatic neuroblastoma, and lymphomas [10, 22].

Round cells arranged in the form of solid strata, minimal amount of cytoplasm, protruding nuclei, no rosette formation, mitoses, and the presence of bone structures
are the characteristic histological signs of ES [13]. Patient’s age and tumor localization facilitate diagnosis. Immunohistochemistry testing reveals vimentin and CD99 expression with the characteristic membrane staining [19]. The tests show negative results for the expression of desmin, S-100 protein, chromogranin (neuronal marker), lymphoid markers CD20 and CD3. ES differs from neuroblastoma, rhabdomyosarcoma, lymphoma, etc. by the absence of expression of synaptophysin, desmin, leukocyte antigen, and other markers [12, 18].

The immunohistochemistry and FISH studies, which determine translocation [(t(11; 22) (q24; q12)] that is typical of ES, are diagnostic and important prognostic factors [12, 16].

The immunohistochemistry test allows one to refine the tumor type: CD99 protein expression was observed in all cases [2, 17].

It is important that primary and metastatic tumors are virtually identical in terms of immunohistochemical parameters: the same proteins were expressed in both groups [15, 16].

However, there were some indirect factors that made the primary tumors differ from the metastatic ones. The Ki-67 labeling index was higher in patients with metastatic tumors and the number of mitoses was greater, which correlates with the more aggressive and malignant tumor growth and shorter life expectancies of patients as compared to the group of patients with primary ES [12, 16].

The combined treatment for both primary and metastatic ES is currently considered to be the optimal treatment method [21].

The aim of a surgical intervention is to reduce the tumor size as much as possible. In 14 observations with primary ES of the skull described by K. Desai et al. [13] in 2000, subtotal and total removal of the tumor was performed in 9 and 5 cases, respectively. A relapse was observed in only one patient after the total resection of the tumor. Hence, tumor resection should be as radical as possible within the admissible safety limits [6].

The choice for surgical approach is mostly determined by tumor localization. While only transcranial approach can be used in patients with convexital lesions, endoscopic transnasal interventions can be performed in patients with tumors of the skull base (in particular, if the chiasm-sellar region is affected) [21].

Treatment of ES is multimodal; it comprises the maximum resection of the tumor followed by radiation and chemotherapy [1, 24].

Radiation therapy is used after surgical interventions as an adjuvant method for patients with primary and metastatic tumors. The recommended scheme for radiation therapy is 1.5–2 Gy/day, 5 days per week, TBD 40–50 Gy [12].

The prognosis for patients with ES used to be unfavorable when surgical intervention and radiation therapy were the only treatment options; the 5-year survival rate was less than 8–15% [8]. In 1974, the combination of postoperative multimodal chemotherapy and radiation therapy was implemented by Rosen. The 5-year survival rate increased from 10 to 55–60%. The round cell therapy (RCT) I, which consisted of 6 cycles of cisplatin and etoposide, vincristin, doxorubicin and cyclophosphamide prescribed at a 3-week interval was used until 1990. The chemotherapy was followed by radiation therapy with TBD 40–50 Gy. When the RCT-I option was used, the 5-year survival rate was 20%. The RCT-II protocol has been used since 1993, which increased the 5-year survival rate to 50%. This protocol consists of the induction phase comprising two cycles of iodophosphamide and etoposide, vincristin, doxorubicin, and cyclophosphamide prescribed at 3-week intervals. Radiation therapy with TBD 40–50 Gy is used 8–9 weeks after the induction therapy had been completed. The supportive chemotherapy consists of 6 cycles of vincristin, doxorubicin, cyclophosphamide, and dacarbazine; it is further prescribed at 3-week intervals [1, 14, 25].

The presence of distant metastases by the time of diagnosis is the most unfavorable prognostic factor in patients with ES [26]. The other unfavorable factors include patient’s age older than 10 years; tumor size larger than 200 ml; “median” localization (e.g., of the pelvis and spine), low efficiency of chemotherapy [14].

The treatment outcomes in patients with ES become better with time. According to Mayo Clinic reports, the 5-year survival rate during the period from 1950 to 1968 was as low as 21.8% [15, 23]. According to the reports in 2000, the 5-year survival rate in patients with ES in the same hospital reached 74%. The 50–80% 2-year survival rate without any signs of the disease after the complex therapy was reported in another large series of observations [14].

The primary ES of the skull base has a more favorable course as compared to the metastatic tumor. Among 14 patients, 8 (57.1%) ones survived five years. It is a good outcome as compared to the literature data. The patients with cranial metastases usually do not survive five years, regardless of the therapy options [1].

**Conclusions**

Both metastatic and primary ES of the skull base occur with almost identical frequencies. The primary tumors are typical of patients younger than 3 years, while the metastatic tumors are observed in patients older than 11 years. There is past medical history of primary tumor in all cases of metastases to the skull base. The clinical presentation usually consists of the symptoms of cranial nerve lesions. There are no pathognomonic X-ray signs that enable one to differentiate between the primary and metastatic ES. The higher Ki-67 labeling index is the only difference when conducting a pathomorphology test. Combined treatment for both the primary and metastatic tumors is applied according to the same scheme and allows one to achieve relatively good outcomes. The prognosis is more favorable in patients with primary ES.
The tumor was primary in 5 cases and was of metastatic origin in the remaining 4 cases. A comparative analysis of the metastatic and primary tumors was made in this study. The authors compared the morphological, immunohistochemical, and genetic presentations of the primary and metastatic tumors and showed them to be identical. No differences between these two groups have been detected, which at least theoretically and in practice supports the hypothesis of a common origin from neuroectodermal elements. The data gained may be useful in the differential diagnosis of the primary and metastatic forms of ES, including intracranial tumor localization.

Commentary

While being the second most frequent malignant bone cancer, Ewing’s sarcoma (ES) affects skull bones in 9% of cases. It is a relatively rare tumor in neurosurrounds. The data in literature devoted to ES of the skull mostly include the description of sporadic cases. ES is known to have a rather aggressive course and to be manifested multilocally in 30% of cases.

This study is of significant interest due to the fact that it presents a thorough comparative analysis of the metastatic and primary ES of the skull base in patients operated on in the same hospital. It is a part of the problem of skull base surgery. Despite the advance in modern neurosurgery, it is not radiologically removable of tumors of the skull base is not always feasible. The authors have analyzed 9 cases of ES of the skull base and operated on in the Burdenko Neurosurgical Institute. The tumor was primary in 5 cases and was of metastatic origin in 4 cases.

The problem of differential diagnosis of the primary and metastatic ES of the central nervous system is rather topical from the perspective of disease prognosis, since the prognosis in patients with metastatic ES to the CNS is known to be unfavorable using any treatment methods and the life expectancy of patients is less than 5 years. In patients with primary ES, the use of radiation therapy combined with polychemotherapy enables one to increase the life expectancy of patients by over 5 years.

The tumor pathomorphology was thoroughly described in this study. The authors compared the morphological, immunohistochemical, and genetic presentations of the primary and metastatic tumors and showed them to be identical. No differences between these two groups have been detected, which attests to the identical genetic and pathomorphological bases of the tumors, on one hand, and substantiates that the same treatment regimen can be used, on the other hand.

The identical treatment strategy was used: the possibly complete radical removal of the tumor followed by radiation- and chemotherapy was performed. Of course, the aspects of the surgical strategy (how to attain the maximum reduction of tumor size) are of the most significant interest for neurosurgeons. In patients with ES, the possibly complete radical removal of the tumor is the key criterion for successful treatment. However, with allowance for the not very favorable prognosis for patients with metastatic lesions, surgeons should not seek the “invalidizing” radicality that results only in “treating the tomography scans”. The radiosurgical techniques should presumably be emphasized in these cases.

G.G. Shaginyan (Moscow)