Volume 1 Issue 1
www.escientificlibrary.com

ES Journal of Clinical Medicine

"Little angel battling for life": A case report of Ewing sarcoma

Case Report

Sheetal Mujoo[1], Megha Gupta[2], Alok Dubey[3]* and Imran Khalid[4]

[1]*Department of Oral Medicine and Radiology Jazan University, K.S.A*
[2]*Department of Pedodontics and Preventive Dentistry Vyas Dental College and Hospital India.*
[3]*Department of Preventive Dental Sciences Jazan University, K.S.A*
[4]*Department of Oral and Maxillo- Facial Surgerying Khalid Universit Saudi Arabia*

Received: Jan 27, 2020; **Accepted:** Feb 20, 2020; **Published:** Feb 22, 2020

***Corresponding author:** Alok Dubey, Department of Preventive Dental Sciences, College of Dentistry Jazan University, K.S.A

Abstract

Ewing's sarcoma (ES) is a rare malignant tumor that primarily affects the skeleton system in children and young adults. The most common symptoms are pain and swelling in the affected area. History of trauma is often reported. Clinical, radiographic, histologic and immunohistochemical investigations are necessary for the diagnosis of this disease. Early diagnosis is very important for the better prognosis of the patient. This case reports a rapidly expanding mass on the right side of the face of a 9 year old Indian boy following an injury; which was diagnosed as ES of the maxilla.

Prompt and early diagnosis is essential for a good prognosis as this lesion shows aggressive behavior with non-specific clinical findings.

Keywords

Ewing's sarcoma, CD99, maxilla, immunohistochemistry

Introduction

ES is a rare malignant small round cell tumor that affects the skeletal system [1]. It was first described by James Ewing in 1921 [2]. It is a part of ES family of tumours (ESFT) that also includes peripheral neuroectodermal tumour (PNET), neuroepithelioma and Askin's tumour. It is an aggressive tumor showing rapid growth and metastasis [3].

It accounts for 4-10% of all primary bone cancers affecting adolescents and young adults [4]. The lesion arises in the medullary portions of the bone and spreads to the endosteal and later to the periosteal surface [5].

Males are affected twice more than females. The tumor is mainly seen in the long bones and pelvis; with head and neck region being an unusual site of occurrence [6]. Less than 3 % of all ES originate in the maxillofacial region [7]. Mandible is more commonly affected than maxilla.

Immunohistochemistry and molecular assays for chromosomal translocation are the mainstay of diagnosis. ES has the most unfavourable prognosis of all primary musculoskeleton tumors [8].

A combined approach including surgery, radiotherapy and chemotherapy is the best approach for the treatment of such patients.

Case Report

A ten year old male patient reported to our department with the chief complaint of pain and swelling in the upper and lower right back region of the jaw and face since last 6 months. The patient was conscious, cooperative with a

Table 1: Routine blood investigations

	Observed value	General value
Hb %	9 gm %	Males – 13-17 %
TLC	7800/ cumm	4,000-11,000 /cumm
DLC		
Neutrophils	54 %	50-70%
Lymphocytes	44%	25- 45%
Eosinophils	02%	1- 6%
RBC Count	3.8 million	Males- 4.5-6.5 million/cumm
Bleeding time	1 minute	1-5 minutes
Clotting time	4.5 minutes	2-6 minutes

normal gait, but weak and pale. The patient complained of fatigue, fever and anorexia (Figure 1).

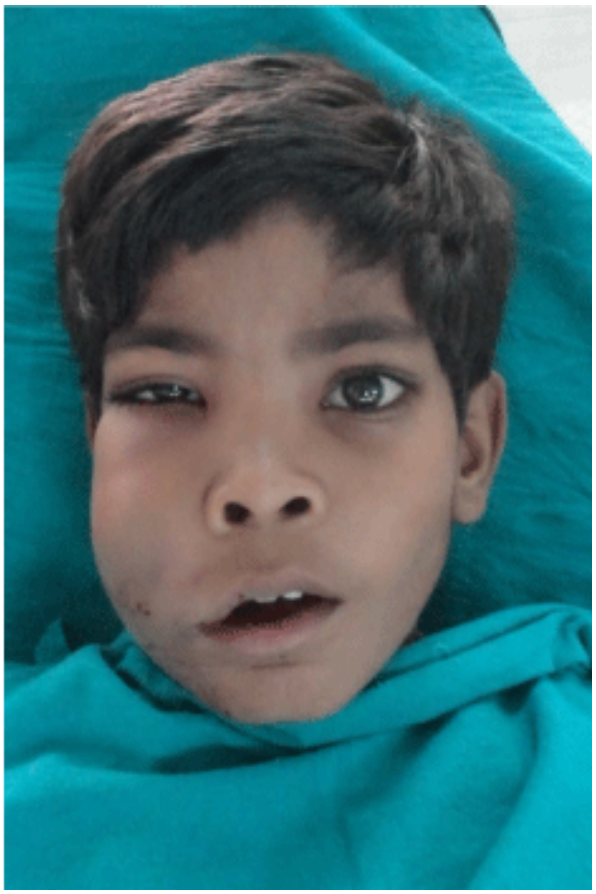

Figure 1: Photograph at the initial examination showing swelling on the right face

The patient suffered trauma 6 months back over the right zygomatic region due to interpersonal violence. After a few days of trauma, swelling appeared in the same region, which gradually increased to the present size. The swelling was associated with pain; which was sharp, continuous and subsided after taking medication. Just 2 days prior to our visit, an incisional biopsy was performed at a private clinic, following which the swelling had increased and there was fluid and blood discharge from the lesion intraorally. The patient did not report any systemic illness in the family. The vital signs were normal (Figure 2).

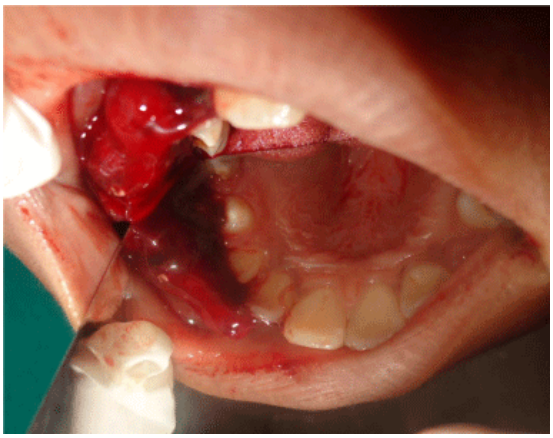

Figure 2: Intraoral photograph taken at the initial examination showing the tumor mass covering the occlusal surface of maxillary teeth.

Extra-oral examination revealed a solitary diffuse swelling on the right side of the face extending medio-laterally from the facial midline to the tragus of right ear. It extended from the supra-orbital ridge to the lower border of the mandible, measuring 6x8 cm longest dimension. The skin overlying the swelling was stretched, red, erythematous. However, no secondary changes were observed. The swelling was firm and hard in consistency, tender on palpation with an elevated temperature. It was non-fluctuant, and could not be compressed or reduced (Figure 3 & 4).

Intra-oral examination revealed a firm swelling with well-defined borders covering the occlusal surface of right maxillary teeth extending mesio-distally from the right

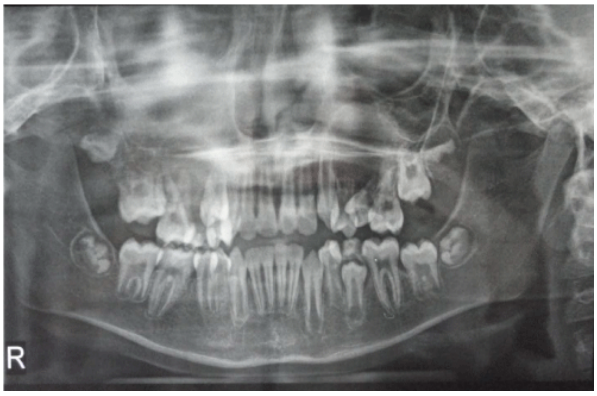

Figure 3: Panoramic radiograph showing solitary lesion with irregular, diffuse ragged borders involving right maxilla

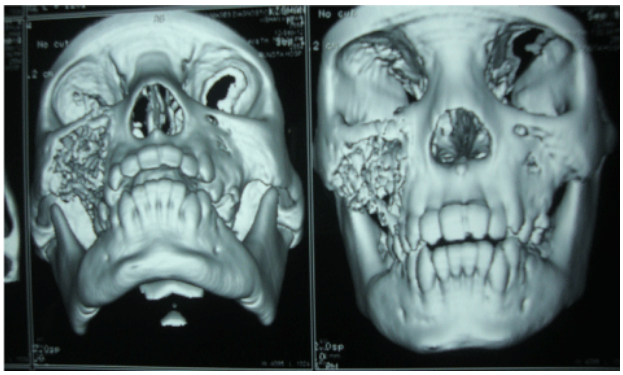

Figure 4: CT Scan: Sagittal view

central incisor to the maxillary tuberosity in the posterior. Superio-inferiorly, the swelling extended from the buccal vestibule to the occlusal surface of the maxillary teeth and was bluish-red in color. All the inspectory findings were confirmed on palpation. The swelling was erythematous, tender, firm-hard, with bleeding on slight provocation. The patient also complained of numbness in that region. The right sub-mandibular lymph nodes were palpable, mobile and tender. The patient exhibited mixed dentition, with poor oral hygiene.

The routine blood investigations were advised and are presented in Table 1. The panoramic radiograph showed a solitary lesion which was irregular, diffuse, mixed radiolucent and radio-opaque with ragged borders. The lesion extended mesio-distally from the lateral aspect of nasal septum to the mesial aspect of maxillary right third molar tooth. Superio-inferiorly, it extended from the floor of the orbit upto the interdental bone of the right maxillary first premolar to the third molar. Lesion was destructive in nature, with a little induction of bone formation and loss of trabecular pattern. Root resorption and destruction of the supporting bone of the maxillary posterior teeth was also seen. The outline of the maxillary sinus could not be appreciated on the right side. The trabecular pattern around the right maxillary molar teeth showed few septas and gave a honey – comb like appearance. The characteristic onion peel appearance or "sun ray" pattern was not seen in our case (Figure 5).

CT scan showed a large lytic lesion involving the right maxilla, along with internal areas of new bone formation involving the right maxilla with involvement of all margins and right maxillary sinus. Erosion of the medial wall of the sinus was seen bulging into the right side of nasal cavity. This erosion extended posteroinferiorly into the

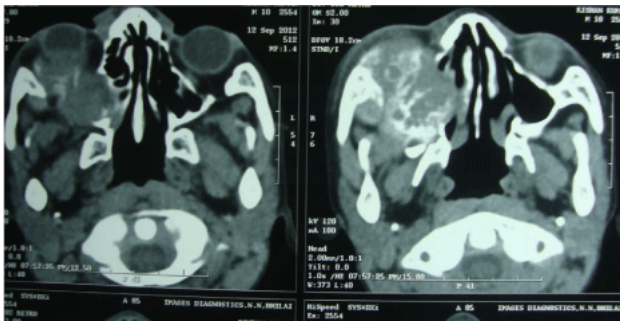

Figure 5: Axial CT image

infratemporal fossa and anteriorly into the soft tissues of cheek.

The lesion also involved the alveolar margins along with soft tissue swelling of the face. The mass infiltrated into the right orbit with involvement of retrobulbar fat and displacing the eyeball (Figure 6).

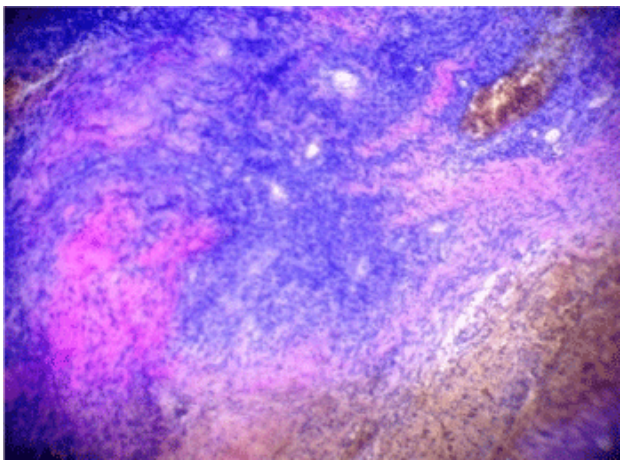

Figure 6: Histopathological view

Histopathological examination showed haphazard proliferation of ulcerated overlying stratified squamous epithelium with underlying connective tissue stroma which is hypercellular with numerous small capillaries. Lobular architectural arrangement of numerous round to oval cells with dark nucleus and eosinophillic cytoplasm is seen around these capillaries. Few of these cells are acute inflammatory in nature. Numerous vascular spaces with extravasation and melanin pigmentation and bundles of neural tissue are also seen. Intracytoplasmic glycogen showing positivity for PAS staining was absent in our case. Pleomorphism and areas of necrosis were also not seen.

Immunohistochemistry exhibited strong immunereactivity against CD99 and vimentin which

reaffirmed the diagnosis of ES. The patient was advised molecular diagnosis to detect the characteristic chromosomal translocation using Florescence in situ hybridization, but he expired before the test could be done. Histopathological and immunohistochemical findings support the diagnosis of ES.

Discussion

ES is the 2nd most common malignant bone tumor in infancy and childhood after osteosarcoma and represents 1% of all the malignant tumors in children [9].

Ewing believed the tumor to be of endothelial origin, but currently the tumor is thought to have a neuroectodermal origin, since it has similar reciprocal translocation as seen in peripheral neuroectodermal tumour (PNET). The immature reticular cells and primitive mesenchymal cells of the bone marrow have also been proposed as possible sites of origin of tumor [10]. According to WHO, Ewing sarcoma/peripheral neuroectodermal tumor (ES/PNET) both refer to the same process since they correspond to same genetic alteration (translocation 11:22) in 95% of cases [11].

85-95% of such cases, undergo oncogenic chromosomal translocations. t(11;22) (q24;q12); which results in the fusion of EWS/FLI-1(Ewing Sarcoma/Friend leukemia integration 1 transcription factor) genes. This gene arrangement causes a fusion product which functions as an oncogenic aberrant transcription factor with structural variability and potentially prognostic impact. In the remaining 10-15% of cases, the translocation t (21; 12) (22;12) is seen [12].

ES comprises of about 4-6% of all primary bone tumours. It originates in the marrow cavity and is found in the epiphysis of long and flat bones. Though rare in the head and neck region, when it occurs the mandible is more frequently affected than maxilla. This makes our case, as rarest of the rare.

Systemic symptoms include fever, lymphadenopathy, weight loss and anemia.[4] The common presenting signs and symptoms in the maxillofacial region are swelling, pain, dental displacement, loose teeth, paresthesia, root resorption, destruction of dental follicle, premature exfoliation, trismus and toothache [13]. Swelling is invariably present in all the cases, and was seen in our case too.

Radiographically, ES presents as a lytic, poorly defined lesion with the displacement of unerupted tooth follicles. Widening of PDL space, loss of the continuity of lamina dura, root resorption and displacement of teeth are commonly seen. The tumor has poorly defined limits and no peripheral sclerotic reaction [14]. “Onion peel” laminar periosteal reaction is a common radiological feature of ES involving long bones, but is rarely seen in jaws and was not seen in our case too [15]. Moreover, the periosteal laminations would be difficult to visualize because of the complex anatomy of the jaws. Our case showed an irregular, diffused, solitary mixed radioopaque radiolucent lesion.

Microscopically, ES is composed of small, round cells arranged in various patterns like sheets, cords, strands and nests. The cells have minimal cytoplasm which is pale staining, ill-defined and irregularly vacuolated due to presence of intracellular glycogen deposits. Nucleus is round to oval, hyperchromatic and vesicular. Areas of necrosis and hemorrhage may be seen in the stroma and these have been associated with poor prognosis. Seventy five percent of cases show positivity to Periodic Acid Schiff (PAS) staining due to the presence of the intracytoplasmic glycogen granules, though it is not pathognamic of this disease.

The first assessment should be imaging of the suspected tumor by MRI preferably, encompassing the entire involved bone or compartment. It should be done before the occurrence of bleeding/edema from biopsy. However, in the routine clinical practice this might be difficult as the dentist wouldn’t anticipate this rare tumor in the initial assessment. In addition, in the developing countries, the cost factor is also an important issue.

The dentist may be the first person to see the ES of the head and neck region, hence they must carefully evaluate patient to arrive at the correct diagnosis by looking for signs and symptoms that point towards a malignant disease. Features pointing towards malignancy would include chin paresthesia, absence of suppuration, absence of dental lesions causing infection and possible general health alterations in the patient. These features will help in differentiating the lesion from a dental infection.

ES family of tumours can be distinguished by ultrastructural features. Transmission electron microscopy of classical ES demonstrated densely packed undifferenciated tumour cells with cytoplasmic glycogen

and scarce organelles and absence of neural differenciation such as dense core neurosecretory granules, neuritic processes and microtubules. [16]

ES should be differentially diagnosed from other round cell tumours like small cell osteogenic sarcoma, mesenchymal chondrosarcoma, Rhabdomyosarcoma, Neuroblastoma, Desmoplastic small round cell tumour and Lymphoblastic lymphoma.

A panel of immune markers are needed to differentially diagnose these small round cell tumours which are vimentin, CD99, Leucocyte common antigen (LCA), Pan-cytokeratin, Desmin, MYOD1/ Myogenin, chromogranin and S-100 protein.

The most useful, though non-specific marker is CD-99, which produces a strong diffuse membranous staining pattern in "chain-mail pattern" in up to 98% cases. CD-99 is a; encoded by the MIC2 gene located at the end of the short arm of the X and Y chromosome. Gene expression profiling studies suggest that CD99 affects differentiation and malignancy of round cells [16].

Cluster of differenciation 99 (CD99), is a 32-kDa integral membrane glycoprotein protein encoded for by the myc2 gene located on the short arm of chromosomes X AND Y, which is highly sensitive for small blue round cell tumors in children, particularly ES/PNET, Lymphoblastic lymphoma and lymphoblastic leukemia [17]. Positivity to CD99, with membranous accentuation is a characteristic of ES. Lymphoblastic lymphoma is also strongly immunoreactive to CD99 with the same membranous pattern. However, it is immunereactive to leukocyte common antigen (LCA) also while ES is not.

Rhabdomyosarcoma is also immunereactive to CD99 and it shows focal, weak cytoplasmic staining. CD-99 positivity can also be seen in lymphoblastic lymphoma and mesenchymal chondrosarcoma. Amongst these, lymphoblastic lymphoma is composed of lymphoid cells, intermixed with round cell of varying size and cytoplasmic contents. The reticulin stain is often positiveand cells are LCA positive.

Mesenchymal chondrosarcoma has biphasic pattern and is composed of scattered areas of cartilage, and highly vascular mesenchymal tissue composed of undifferentiated spindle cells or round cells with cytoplasm. Blending of islands of cartilage with cellular areas is observed. This tumour also shows Neuron Specific Enolase (NSE) positivity [18]. Hence, ES can be differentiated from these two based on H& E and positivity for other markers.

FL1 nuclear positivity has been reported in 71% - 84% cases of ES/PNET. FL-1 positivity can help in distinguishing ES from other CD99 positive round cell tumours and antibodies to FLI-1 may play a valuable adjunctive role in the diagnosis of ES/PNET [19].

Our case showed strong membranous positivity for CD99 and Vimentin; however the tumour cells were negative for NSE and LCA.

The treatment of ES comprises of multimodal therapy comprising of chemotherapy, surgery and radiotherapy. CT scan of the chest to detect pulmonary metastasis, bone scintigraphy to detect bony metastasis, marrow aspirate and biopsy are important diagnostic tools. The chemotherapeutic agents commonly used are vincristine, doxorubicin, cyclophosphomide, ifosfamide and actinomycin-D. Concerns about the dynamics of the growing facial skeleton of pediatric patient should be kept in mind when reconstructive surgery for tumor is planned.

Molecular diagnosis using either fluorescent in-situhybridization (FISH) to detect the fusion gene, or reverse transcriptase (RT-PCR) to detect its transcript, should be done [20]. Diagnosis of ES requires atleast 2 neuronal markers and evidence of translocation 11:22 [21].

Conventional chemotherapy is ineffective in few patients with localized tumors and in patients with metastases. Hence, biologically based approaches to the treatment have been developed. These include EWS-FLI1 fusion protein, RNA helicase A, Insulin-like growth factors (IGFs) and type 1 receptor, Rapamycin and analogues, Fenretinide.

ES has poor prognosis because of rapid hematogenous spread and lung metastasis. Prognosis depends upon the presence of metastatic disease at the time of diagnosis, early tumour recurrence, anatomic site of involvement and tumour size. ES of the maxilla usually has the worst prognosis because of the sinus and orbital involvement. The same was seen in our case. Prognosis of the patients of Ewing's sarcoma has markedly improved with the advent of multimodal therapy.

Conclusion

Ewing's Sarcoma is a diagnostic challenge because of

many overlapping clinical, radiographic, histopathological and immunohistochemical features with malignant round cell tumours. It can mimic odontogenic infection also. Histopathological investigation is mandatory. An immunohistochemical study is the key to specific diagnosis. The management requires a multidisciplinary approach between oncologist and pedodontist who would probably be receiving the patient early at diagnosis. Dental professional has an important role in the prompt diagnosis and referral for the multidisciplinary care of patients with ES.

Consent

Written informed consent was obtained from the patient's parents for the usage of the information and accompanying images for research purposes.

References

1. Balamuth NJ, Womer RB. Ewing's sarcoma. Lancet Oncol, 11(2):184-92, 2010.
2. Potgar G. Ewing's tumors of the jaws. Oral Surg Oral Med Oral Pathol, 39:505-12, 1970.
3. Deshingkar S, Barpande S, Tupkari J. Ewing's sarcoma of the zygoma. J Oral Maxillofac Pathol., 13(1):18-22, 2009.
4. Brazão-Silva MT, Fernandes AV, Faria PR, Cardoso SV, Loyola AM. Ewing's sarcoma of the mandible in a young child. Braz Dent J, 21(1):74-9, 2010.
5. White SC and Pharoah MJ. Oral Radiology. Principles and Interpretation. 7th edn, Elsevier Publication, 410-456, 2013.
6. Fonseca AS, Mezzalira R, Crespo AN, Bortoleto AE Jr, Paschoal JR. Ewing's sarcoma of the head and neck. Sao Paulo Med J., 9; 118(6):198-200, 2000.
7. Talesh KT. Motamedi MHK, Jeihounian M. Ewing's sarcoma of the mandibular condyle. Report of a case. J Oral Maxillofac Surg, 61(10): 1216-1219, 2003.
8. Iwamoto Y. Diagnosis and treatment of Ewing's sarcoma. Jpn J Clin Oncol, 37:79-89, 2007.
9. Esiashvili N, Goodman M, Marcus RB Jr. Changes in incidence and survival of Ewing sarcoma patients over the past 3 decades: Surveillance Epidemiology and End results data. J Pediat Hematol Oncol, 30:425-30, 2008.
10. Arndt CA, Rose PS, Folpe AL, Laack NN. Common musculoskeletal tumours of childhood and adolescents. Mayo Clin Proc, 87: 475-87, 2012.
11. Hadju SI. The enigma of Ewing's sarcoma. Ann Clin Lab Sci, 36:108-10, 2006.
12. Przybyl J,Kozak K, Kosela H, Falkowski S, Switaj T, Lugowska et al. Gene expression profiling of peripheral blood cells : new insights into Ewing sarcoma biology and clinical applications. Med Oncol, 31(8):109, 2014.
13. Margaix-Muñoz M, Bagán J, Poveda-Roda R. Ewing sarcoma of the oral cavity. A review. J Clin Exp Dent, 1; 9(2):e294-e301,2017.
14. Krishna KB, Thomas V, Kattoor J, Kusumakumari P. A radiological review of Ewing's sarcoma of mandible: a case report with one year follow-up. Int J Clin Pediatr Dent, 6(2):109-14, 2013.
15. Gupta S, Gupta OP, Mehrotra S, Mehrotra D. Ewing sarcoma of the maxilla: A rare presentation. Quintessence Int, 40:135-40, 2009.
16. Hameed M. Small round cell tumors of bone. Arch Pathol Lab Med, 131(2):192-204, 2007.
17. Rocchi A, Manara MC, Sciandra M, Zambelli D, Nardi F, Nicoletti G et al. CD99 inhibits neural differentiation of human Ewing sarcoma cells and thereby contributes to oncogenesis. J Clin Invest,120(3):668-80, 2010.
18. Sinha DK, Jha NK, Yadav SK, Yadav J, Sinha R. ewing's sarcoma of mandible: a very rare disease and review of Indian literature. Indian J Surg Oncol, 5(1):81-84, 2014.
19. Folpe AL, Hill CE, Parham DM, O'Shea PA, Weiss SW. Immunohistochemical detection of FLI-1 protein expression :A study of 132 round cell tumours with emphasis on CD99 –positive mimics of Ewing's sarcoma/primitive neuroectodermal tumour. Am J Surg Pathol, 24(12); 1657-62,2000.
20. Kovar H, Le Deley M, Delattre O, et al. Impact of EWS-FLI11 fusion type on disease progression in Ewing's sarcoma: prospective results from the cooperative Euro-E.W.I.N.G. 99 trial. Proc Annu Meet Am Assoc Cancer Res, abstr 5680, 2009.
21. Mamede RM, Mello FV, Barbieri J. Prognosis of Ewing's sarcoma of the head and neck. Otolaryngol Head Neck Surg, 102:650-53, 1990.