JOURNAL OF ORAL MEDICINE, SURGERY, PATHOLOGY, BIOLOGY

A rare case of Pediatric Hemangiopericytoma of the oral cavity: A case report and review of literature

Dr. Pinhaj Ahmed Sherashiya,[1] Dr Mihir Nayak,[2] Dr Yogesh TL,[3] Dr. Nonita Ramesh[4]

1. Senior Oral Diagnostic Oncologist, Karnataka Cancer Society, Vyalikaval, Malleshwaram, Bengaluru-560003, Karnataka, INDIA.

2. Senior Lecturer, Department of Pediatric and Preventive Dentistry, Sri Rajiv Gandhi College of Dental Sciences & Hospital, Cholanagar, Bengaluru-560032, Karnataka, INDIA

3. Professor, Department of Oral Pathology and Microbiology, Sri Rajiv Gandhi College of Dental Sciences & Hospital, Cholanagar, Bengaluru-560032, Karnataka, INDIA

4. Senior Lecturer, Department of Oral Pathology and Microbiology, Sri Rajiv Gandhi College of Dental Sciences & Hospital, Cholanagar, Bengaluru-560032, Karnataka, INDIA.

Running title: Malignant/Benign vascular connective tissue tumor

Clinical Significance: Hemangiopericytoma (HPC) is an extremely rare tumor of indefinite malignant potential.

Article citation: Pinhaj AhmedSherashiya, MihirNayak, DrYogesh TL, Nonita Ramesh. A rare case of Pediatric Hemangiopericytoma of the oral cavity: A case report and review of literature. JOURNAL OF ORAL MEDICINE, SURGERY, PATHOLOGY, BIOLOGY. 2016; Vol 1, no 1: 83-92

Address for correspondence:

Dr Pinhaz Sherashiya, MDS

No. 1308, 11th B Cross, Vyalikaval, Bengaluru, Karnataka 560003, INDIA.

E mail add: hi_pinhaz@yahoo.com

ABSTRACT:

Hemangiopericytomas (HPC) are rare benign/malignant vascular tumors; therefore, there have been reports of only about 300 new cases ever since Stout and Murray first described it in 1942. Their assumption of its origin from the “Zimmerman’s pericytes” has been abandoned, and instead, it is now considered to be a translocation-associated neoplasm; associated with NAB2-STAT6 gene fusions in a unique positioning on chromosome 12q; and this rearrangement may be a likely major contributor to its pathogenesis. It is now a “Solitary Fibrous tumor (SFT)” or one of its variants.

Presented here is a review of literature of the pathogenesis, clinical, morphological and immunohistochemical details of a case of Pediatric Hemangiopericytoma/ SFT.

Keywords: malignant vascular connective tissue tumor; hemangiopericytoma; pericytes; solitary fibrous tumor; pediatric hemangiopericytoma

INTRODUCTION

Hemangiopericytomas are sarcomas of the soft tissues that originate from pericytes; the mesenchymal cells that partially surround the endothelial cell lining of the capillaries and small veins. They assist in the regulation of blood flow.[1]

Wagner first described the hemangiopericytoma in 1870. Stout and Murray in 1942 described the hemangiopericytoma, as an unusual soft tissue neoplasm, depicting the characteristic well-developed 'staghorn' branching vascular pattern indicating its origin from the pericytes. Since then, 'Solitary Fibrous Tumor (SFT)', [2, 3, 4, 5, 6], which also includes lesions such as the giant cell angiofibroma, and lipomatous HPCs apart from the classic HPCs, [5] has replaced the term 'hemangiopericytoma'.

The growth of this lesion is non-specific and appears similar to numerous other unrelated benign and malignant lesions. Hemangiopericytoma is more of a diagnosis of exclusion.[7]

CASE REPORT

A 9-year-old female patient visited a cancer reference center with a history of a painless growth in the right back tooth region since 10 days. (**Figure 1**)

FIGURE 1

The growth was asymptomatic and unnoticed by the patient in its initial growth phase, but it grew rapidly within a short period, to approximately, triple its initial size. The lesion came to the notice of the guardian only when it started creating problems during oral prophylaxis. The guardian assumed that the lesion was a consequence of trauma during tooth brushing. The lesion was painless, and there was neither tenderness nor bleeding. On intraoral examination, a firm growth about 4 x 5 centimeters in size in the 46-85 regions, that was neither painful nor tender, but fixed to the overlying structures; was observed. (**Figures 2 and 3**) The lymph nodes on the same side were unaffected.

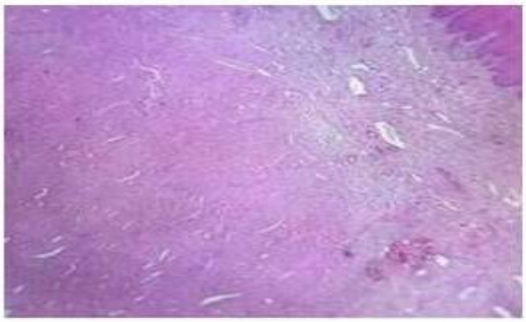
FIGURE 2

FIGURE 3

Occlusal radiograph and the Orthopantomogram showed cuffing radiolucency posterior to 46 about 2 x 1 centimeter in size.

(**Figures4 and 5**)

The provisional diagnosis was Peripheral Giant cell granuloma/Irritational fibroma/Ossifying fibroma. The lesion recurred post biopsy when the lesion aggravated to 3 times its initial size. The patient was referred to a cancer specialty center of the region, and a provisional diagnosis of Hemangiopericytoma (Solitary Fibrous Tumor) was made after observation of the hematoxylin- eosin stained section of the biopsy specimen. The lesion was poorly circumscribed and showed numerous proliferative endothelial lined dilated blood vessels with a "stag horn pattern" surrounded by proliferative plump endothelial cells in sheets and nests. (**Figures 6, 7, 8, 9 and 10)**



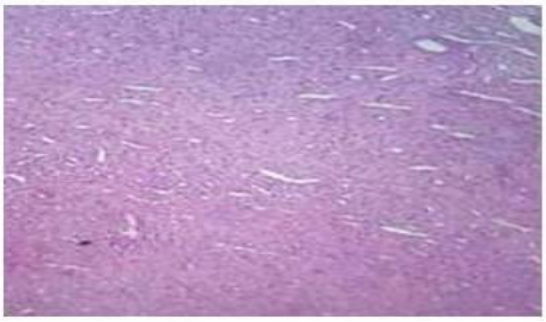


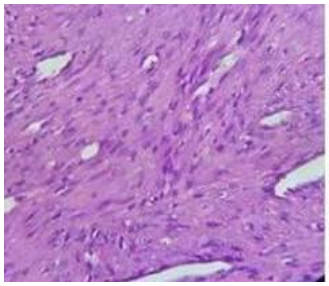
Figure 6: (H and E) superficial epithelial lining and capillaries (scanner)

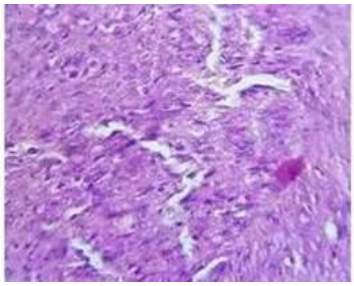
Figure 7: (H and E) "Stag horn" appearance and "stag horn" blood vessels.(scanner)

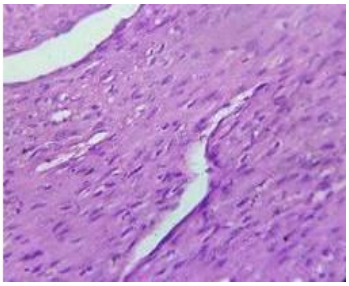
Figure 8: "Stag horn" capillaries with surrounding stroma (10x) "

Figure 9: Vessels appearing as" stag horn" (10x)

Figure 10: Blood vessels in HP (10x) (H and E)







The cells had prominent nuclei without atypia. In certain areas, the cells were tightly packed and showed proliferation in whorls. The patient could not afford the immunohistochemical testing of the sample. The lesion healed after 15 days, following surgical excision with wide margins. Patient was advised regular monthly follow-up visits.

DISCUSSION

Hemangiopericytoma (HPC)/solitary fibrous tumor (SFT) is a rare soft tissue tumor having an inconsistent malignant behavior.

History and description

First recognized by Schmidt in 1937 and then described in 1942, by Stout and Murray this neoplasm, is "tumor of vessels arising from Zimmerman's pericytes".[7,8] Ultrastructural and immunohistochemical studies done, at a later period, identified pericytes in only 1/3 rd of cases of HPCs.[7]The concept of the HPC being a vascular, pericyte-derived tumor has been cast aside and is now considered to be a tumor of fibroblastic origin: the **Solitary Fibrous Tumor.** Both Hemangiopericytomas and Solitary Fibrous Tumors of the soft tissues have been regarded as varying features of the same entity.[14] HPC was the classic or cellular variant ofSFT.

Classification

- **Classified based on course:**

  The SFT may be either extremely
  - Malignant or aggressive or
  - May show a fairly benign behavior that enlarges locally without metastasis.[11]
- **Classified based on age of occurrence:**
  - Infantile:
  - Pediatric HPC or HPC in children.
  - They are of two types namely:
    - Infantile: The tumor that occurredbefore the age of 1 year. The infantile HPC accounts for 3% of all malignant pediatric tumors [16] and
    - After the age of 1 year. The tumor behaved in a fashion very similar to the adult lesion. About 20-35% of them were malignant.[12]
      - Adult [14]
- **Classified based on features:**

  Three classes of the SFT have been identified:
  - Non-HPC neoplasms that may sometimes display HPC-like features (e.g. synovial sarcoma).
  - True, classic or cellular HPC, where there is a clear evidence of myoid/pericytic differentiation. They show a benign clinical course and include tumors such as glomangiopericytoma/myopericytoma, infantile

myofibromatosis (previously called infantile HPC), and a subset of sinonasal HPCs.

- Solitary fibrous tumor (SFT) of the lesional group, which includes fibrous-to-cellular SFTs, and related lesions such as giant cell angiofibroma and lipomatous HPCs.[9]

Etiopathogenesis:

1. **Pericytes**: Extensive studies on the endothelial cells in Hemangiopericytomas had been done, after the discovery of the angiogenic factors like the VEGF, VEGF-1, etc. but none on the pericytes. The importance of the pericytes was recognized only after the vessels lost their pericytes. Pericytes, ['Rouget cells' after their discoverer, Charles Rouget, or 'mural cells' because of their contractile fibers or vascular smooth muscle cells (vSMCs) due to its position around the blood vessels], when lost, causes the vessels to become hemorrhagic and hyperdilated, leading to edema. Angiogenesis in the tumor was also said to be a result of it. Identification of pan-pericytic molecular markers is difficult because of their varied characteristics, functions, and locations within the various organs in which they are originally present. The functions of the pericytes include: guiding the formation of new vessels, sense angiogenic stimuli, exhibit macrophage-like activity, and elicit endothelial survival functions.[13]
2. **vSMCs:** It has generally been accepted that the pericytes and the vSMCs belong to the same lineage. No molecular marker exists, that can clearly identify the pericytes and differentiate them from the vSMCs. A large number of markers used are not specific or constant in their expression. Hence, pericyte would mean any cell that is periendothelial in nature. Ideally, these cells share the basement membrane with the endothelial cells, but this differentiating feature is difficult to identify in all the cases.[14]
3. **Genetic study:**

   The presence of NAB2-STAT6 gene fusion results in the abnormality of the pericytes.Identification of the recurrent gene fusion NAB2-STAT6 has been the molecular hallmark of SFT.[15]The NAB2-STAT6 fusion leads to activation and transcriptional deregulation of EGR1 (Early growth response protein 1) [7, 15]and it has been suggested to play a role in theinitiation of the SFT. Chromosome 12q13 accommodates these two proteins positioned close to each other in opposite directions with a partial overlap of 58 bp of their respective 3′ ends.

   STAT6 is a transcription factor, whereas the NAB2 is a transcriptional repressor, with no capacity to,independently bind DNA. These two proteins have been involved in regulating the vessel formation, in inflammation, fibroblast activation, and collagen production. Transcription factor early growth response 1 (EGR1) is also said to regulate wound healing and fibrosis.[16]

Etiology:

Although the precise etiology is unknown- trauma, hormonal imbalance, and prolonged steroid use has been suggested as factors responsible for the formation of the cellular SFT. Though not widely accepted, hypertension and pregnancy[10] have also been proposed as etiological factors in the development of HPC.[11]

Clinical description

Age: Cellular SFT is common in all ages, but it is especially common in the 6th and 7th decades of life.[7]

5-15% of HPCs occurred in children and young adults.[12]

Sex: There is no definite sex predilection

Site: Although capillaries are present throughout the body, according to Enzinger and Smith, the most predominant site of these lesions is:

- ✓ Lower extremity (35%)
- ✓ Head and neck region (15%), chiefly in the nasal cavity and paranasal sinuses.[4]
- ✓ Followed by pelvis or retroperitoneum (25%)
- ✓ Trunk (14%) and
- ✓ Upper extremity (10%).
- ✓ Esophagus, brain and spine, lung and the breast were also rarely affected

In the head and neck region, the predominantly affected sites were the orbit, nasal cavity, oral cavity parotid gland, pharyngeal space, jugular foramen and the nasal cavity.[7]

Worldwide search literature has identified only 16 cases of HPC in the oral cavity and of them, eight were malignant.

In the oral cavity, the most common location was the tongue and[12] buccal mucosa followed by the lip and the maxillary or mandibular vestibule.[17]

Presentation:

- **Symptoms**: are normally seen in relation to pressure of the lesion onto adjacent structures
- **Signs**: Clinically the lesion presents as a painless, enlarging mass.

Various paraneoplastic syndromes have been associated with cellular SFT, like hypoglycemia, hypophosphatemic osteomalacia and hypertrophic pulmonary osteoarthropathy.[7]

Radiography:

Tomography, radiography, and angiography are not specific for SFT and a solid mass with isodense contrast in T1 is seen on the magnetic resonance imaging.[7]

Histopathology:

HPC has been graded into:

- ✓ Benign,
- ✓ Borderline,
- ✓ Low grade malignant and
- ✓ Overtly malignant.[11]

Two well-defined patterns have been stated by Ensinger and Weiss namely:

- The classic pattern in which there are hypocellular areas alternating with dense cellular areas alternating in a relatively collagenous, vascular stroma and
- Subtle Classic areas in a more uniform sclerotic pattern.[18, 19]

  These lesions usually have a monotonous appearance with a moderate to high cellularity and reduced fibrosis.[1]Pericytes present with few cytoplasmic organelles. [20] Numerous thin-walled “stag horn” interlacing fascicles with dilated, irregularly shaped branching blood vessels and round-to-oval monomorphic, vesicular, elongated hyperchromatic, [11] spindle-shaped[20]tumor cell nuclei with indistinct cytoplasmic borders [11] are also seen.

Features of malignancy in HPC/SFT:

- The presence of a large tumor size of >50mm,
- Disseminated,
- Necrosed with infiltrative margins,[7]
- High cellularity [1](>5%), [18]
- Nuclear pleomorphism,
- With a high mitotic index of more than 4 mitosis/ high power field[5] and
- An absence of irregular areas of sclerosis [18]

The characteristic features of these tumors seen on Computer Tomography or Magnetic Resonance imaging in conjunction with a clinical history of a benign, slow-growing lesion may assist in the diagnosis; but usually, the definitive diagnosis is made only after the tumor resection.[18]

Special stains: Reticulin stains positively the tumor cells, around the blood vessels.[14]

Immunohistochemical markers are used for confirmation of the diagnosis.

- ✓ SMA (smooth muscle actin) is strongly positive in some studies[1] whereas it is considered negative in some others.[20]
- ✓ CD34 is focally positive[7] and usually stains only endothelial cell component, although sometimes there is a diffusion effect in the immediate vicinity.
- ✓ S100 and CD99 are negative.[7]
- ✓ Vimentin is positive
- ✓ STAT6 is positive[10]
- ✓ Rarely and only focally smooth muscle markers; such as desmin is positive as per some authors[4] and negative as per some others. [20]
- ✓ Calponin,
- ✓ CD68 KP1[21]
- ✓ AE1-AE3 positive; as per some[19]and negative as per others. [20]
- ✓ P63 are all positive.[21]
- ✓ A sub-population of tumor cells is also immunoreactive for factor XIIIa and

- ✓ Histocompatibility antigen HLA-DR- positive.[1]
- ✓ CD31, GFAP, and Mib-1 are negative [14.]

The authors have also correlated between the prognoses of the lesion with the number of mitotic figures

Prognosis and grading of lesion:

- o High grade:
  - ▪ <4 mitotic figures per 10 high-power fields
  - ▪ Increased cellularity or necrosis
  - ▪ 10-yearoverall survival- 29%.
- o Moderate grade:
  - ▪ 4 or >4 mitotic figures per high-power field
  - ▪ 10-year, overall survival- 77%.
- o Poor grade:
  - ▪ Tumors showing evidence of necrosis and tumors greater than 6.5 cm in diameter show worst survival
- ◦ Some studies have not been able to draw a relationship between mitotic activity and survival of the patient. [7]

Electron Microscopy

- Wide-ranging basement membrane around every cell
- Bundles of intermediate filaments that are small
- No presence of desmosomes
- No gap junctions present.[20]
- Dense bodies
- Pinocytotic vesicles may be seen

Metastasis:

The rate of metastases: 10%.

Metastases to the bone, lung, liver, pancreas and the regional lymph nodes are said to occur.

Local recurrence: - 40%[7]

The reported rate of recurrence varied from 7 to 20%, with an average time for recurrence being 6–7 years. An incomplete primary excision is a primary factor in recurrence of the lesion.[11]

Differential diagnosis: with epithelial, neural and muscle neoplasms together with prominent vascularization, and they include

- Schwannoma,
- Myofibroblastoma,
- Metastasis From Spindle-Cell Carcinoma
- Lowgrade fibromyxoid sarcoma (especially if the myxoid foci areprominent)
- Synovial Sarcoma, and
- Malignant Peripheral Nerve Sheath Tumor.[7]

Some studies still consider SFT and HPC to be entirely different lesions and the salient differentiating points stated by them include:

- Homogeneously increased cellularity and staghorn-like vessels all throughout the lesion in case of HPC
- Varying cellularity in SFT, which is often thick with presence of keloid-like hyalinization, and
- Mast cells that are absent or reduced in HPC but numerous in SFT.[19]

Treatment

- Wide surgical resection[7]
- Adjuvant radiation therapy[6] in some situations, although the lesion is said to be radioresistant.[21]Postoperative radiation therapy has been recommended in cases of incomplete surgical removal.
- Chemotherapy in cellular SFT has not been clearly determined. Adriamycin alone or in combination produced complete and partial remissions in 50% of the cases. Chemotherapy is mostly useful for preoperative tumor reduction as a postoperative adjunct for tumor metastases and palliation of locally nonoperative lesions.

  Combined therapy with Bevacizumab and temozolomide has been beneficial, and Sorafenib and Sunitinib have also been administered with occasional success. [16]
- Perioperative embolization has been suggested as an adjuvant for decreasing tumor vascularity and size. [7]
- CO_2 laser technique to accomplish both excision and cauterization, and may help in reduction of local relapse and metastasis.[21]

***Declaration of Conflict*: There are no conflicts of interest of any kind**.

***Source of Funding*: The authors declare there is no financial support of any kind**

***Ethical approval*: Written informed consent obtained from the patient for publication of this case report and accompanying images and a copy of the written consent is available for review for the Editors.**

ABBREVIATIONS

NABF1/Zif268 (zinc finger protein 225)/NGFI-A binding protein 2 (nerve growth factor-induced protein A), encoded by the EGR1 gene in humans

SFT---------- Solitary Fibrous Tumor

HPC---------- Hemangiopericytoma

v SMCs---------- Vascular smooth muscle cells

VEGF/VEGF-1---------- Vascular endothelial growth factor/Vascular endothelial growth factor-1

STAT6---------- Signal transducer and activator of transcription 6

EGR1----------Early growth response protein 1

58 bp----------58 base pairs

DNA----------Deoxyribonucleic acid

CT ----------Computer tomography

MRI----------Magnetic resonance imaging

REFERENCES

1. Yasuyuki Michi, Miho Suzuki, Kazuto Kurohara and Kiyoshi Harada. A case of hemangiopericytoma of the soft palate with articulate disorder and dysphagia. International Journal of Oral Science. 2013; 5: 111–114
2. Leon Barnes. Pathology and Genetics of Head and Neck Tumours . World Health Organization, International Agency for Research on Cancer
3. Perrine Marec Berard. Malignant Hemangiopericytoma- Orphanet Encyclopedia. Apr 2004;
4. Su Jin Lee, Seung Tae Kim, Se Hoon Park, Yoon La Choi, Jae Berm Park, Sung-Joo Kim and Jeeyun Lee. Successful use of pazopanib for treatment of refractory metastatic hemangiopericytoma. Clinical Sarcoma Research. 2014; 4:13
5. Elizabeth G Demicco, Min S Park, Dejka M Araujo, et al. Solitary fibrous tumor: a clinicopathological study of 110 cases and proposed risk assessment model. Modern Pathology. 2012; 25: 1298–1306
6. Dimitrios Dragoumis, Klearchos Desiris, Aikaterini Kyropoulou, Maria Malandri, Anthoula Assimaki, and Aris Tsiftsogloua. Hemangiopericytoma/solitary fibrous tumor of pectoralis major muscle mimicking a breast mass.Int J Surg Case Rep. 2013; 4(3): 338–341
7. Paraskevi Tsirevelou, Paschalis Chlopsidis, Ifigenia Zourou, Dimitrios Valagiannis, Charalampos Skoulakis. Hemangiopericytoma of the neck. Head & Face Medicine 2010; 6:23.
8. Angiero F, Signore A, Benedicenti S. Hemangiopericytoma/Solitary fibrous tumor of the oral cavity. Anticancer Res. 2011 Feb;31(2):719-23
9. Rami Archid, Carl Christoph Schneider, Patrick Adam, Ahmed Othman, Derek Zieker, and Alfred Königsrainera. Hemangiopericytoma/solitary fibrous tumor of the greater omentum: A case report and review of the literature.Int J Surg Case Rep. 2016; 23: 160–162
10. Schweizer L, Koelsche C, Sahm F, et al. Meningeal hemangiopericytoma and solitary fibrous tumors carry the NAB2-STAT6 fusion and can be diagnosed by nuclear expression of STAT6 protein.Acta Neuropathol. 2013 May;125(5):651-8
11. Panduranga M. Kamath, S. Vijendra Shenoy, M. Nirupama, T. Vinay Rai. Hemangiopericytoma: A rare sinonasal tumor. Egyptian Journal of Ear, Nose, Throat and Allied Sciences. July 2013; 14(2):151–154
12. Charles D . Bluestone, Jeffrey P . Simons, Gerald B. Healy. Pediatric Otolaryngology. 5th edition. 2000 pages. People\'s Medical Publishing House-USA, 01-Dec-2013; 2nd Vol set: 1817
13. Gabriele Bergers and Steven Song. The role of pericytes in blood-vessel formation and maintenance. Neuro Oncol. 2005 Oct; 7(4): 452–464
14. Annika Armulik, Guillem Genové and Christer Betsholtz. Pericytes: Developmental, Physiological, and Pathological Perspectives, Problems, and Promises. Developmental Cell. 16 August 2011; 21(2): 193–215

15. Rob JC Vogels, Myrella Vlenterie, Yvonne MH Versleijen-Jonkers, et al. Solitary fibrous tumor – clinicopathologic, immunohistochemical and molecular analysis of 28 cases. Diagnostic Pathology. 2014; 9:224
16. Sarah Barthelme, Helene Geddert, Carsten Boltze, et al.Solitary Fibrous Tumors/Hemangiopericytomas with Different Variants of the NAB2-STAT6 Gene Fusion Are Characterized by Specific Histomorphology and Distinct Clinicopathological Features .The American Journal of Pathology. April 2014, ; 184(4):1209–1218
17. Enrique Palacious, Santiago Restrepo, Luciano Mastrogiovanni, Giovanni Lorruso, Rafeal Rojas. Sinonasal hemangiopericytomas: Clinicopathologic and imaging findings- Ear, Nose & Throat Journal. Feb 2005; 84(2): 99-102
18. Ian Ganly, MD, Snehal G. Patel, Jatin Shah, et al. Solitary Fibrous Tumors of the Head and Neck. A Clinicopathologic and Radiologic Review. Arch Otolaryngol Head Neck Surg. 2006;132(5):517-525
19. Esther M. O'Regan,Vijay Vanguri, Carl M. Allen,Lewis Roy Eversole, John M. Wright,and Sook-Bin Woo. Solitary Fibrous Tumor of the Oral Cavity: Clinicopathologic and Immunohistochemical Study of 21 Cases. Head Neck Pathol. 2009 Jun; 3(2): 106–115
20. Wael Al-Daraji, Ehab Husain, Bettena G Zelger, Bernhard Zelger.A Practical and Comprehensive Immunohistochemical Approach to the Diagnosis of Superficial Soft Tissue Tumors. Int J Clin Exp Pathol. 2009; 2(2): 119–131.
21. Emiliano Maresi, Silvia Tortorici, Maria Campione, et al. Hemangiopericytoma of the oral cavity after a ten-year follow-up. Annals of Clinical & Laboratory Science. 2007; 37(3): 274-279