OPINION REVIEW
4280  Role of monoclonal antibody drugs in the treatment of COVID-19
   Ucciferri C, Vecchiet J, Falasca K

MINIREVIEWS
4286  Review of simulation model for education of point-of-care ultrasound using easy-to-make tools
   Shin KC, Ha YR, Lee SJ, Ahn JH
4303  Liver injury in COVID-19: A minireview
   Zhao JN, Fan Y, Wu SD

ORIGINAL ARTICLE
Case Control Study
4311  Transanal minimally invasive surgery vs endoscopic mucosal resection for rectal benign tumors and rectal carcinoids: A retrospective analysis
   Shen JM, Zhao JY, Ye T, Gong LF, Wang HP, Chen WJ, Cai YK
4320  Impact of mTOR gene polymorphisms and gene-tea interaction on susceptibility to tuberculosis

Retrospective Cohort Study
4331  Establishment and validation of a nomogram to predict the risk of ovarian metastasis in gastric cancer: Based on a large cohort
   Li SQ, Zhang KC, Li JY, Liang WQ, Gao YH, Qiao Z, Xi HQ, Chen L

Retrospective Study
4342  Predictive factors for early clinical response in community-onset Escherichia coli urinary tract infection and effects of initial antibiotic treatment on early clinical response
   Kim YJ, Lee JM, Lee JH
4349  Managing acute appendicitis during the COVID-19 pandemic in Jiaxing, China
   Zhou Y, Cen LS
4360  Clinical application of combined detection of SARS-CoV-2-specific antibody and nucleic acid
   Meng QB, Peng JJ, Wei X, Yang JY, Li PC, Qu ZW, Xiong YF, Wu GJ, Hu ZM, Yu JC, Su W
4370  Prolonged prothrombin time at admission predicts poor clinical outcome in COVID-19 patients
### Contents

**World Journal of Clinical Cases**

Semimonthly Volume 8 Number 19 October 6, 2020

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>4380</td>
<td>Percutaneous radiofrequency ablation is superior to hepatic resection in patients with small hepatocellular carcinoma</td>
<td>Zhang YH, Su B, Sun P, Li RM, Peng XC, Cai J</td>
</tr>
<tr>
<td>4388</td>
<td>Clinical study on the surgical treatment of atypical Lisfranc joint complex injury</td>
<td>Li X, Jia LS, Li A, Xie X, Cui J, Li GL</td>
</tr>
</tbody>
</table>

**Clinical Trials Study**

4410  Optimal hang time of enteral formula at standard room temperature and high temperature  

Lakananurak N, Nalinthassanai N, Suansawang W, Panarat P

**META-ANALYSIS**

4416  Meta-analysis reveals an association between acute pancreatitis and the risk of pancreatic cancer  

Liu J, Wang Y, Yu Y

**SCIENTOMETRICS**

4431  Global analysis of daily new COVID-19 cases reveals many static-phase countries including the United States potentially with unstoppable epidemic  

Long C, Fu XM, Fu ZF

**CASE REPORT**

4443  Left atrial appendage aneurysm: A case report  

Belov DV, Moskalev VI, Garbuzenko DV, Arefyev NO

4450  Twenty-year survival after iterative surgery for metastatic renal cell carcinoma: A case report and review of literature  

De Raffele E, Mirarchi M, Casadei R, Ricci C, Brunocilla E, Minni F

4466  Primary rhabdomyosarcoma: An extremely rare and aggressive variant of male breast cancer  

Satală CB, Jung I, Bara TJ, Simu P, Simu I, Vlad M, Szodorai R, Gurzu S

4475  Bladder stones in a closed diverticulum caused by *Schistosoma mansoni*: A case report  

Alkhamees MA

4481  Cutaneous ciliated cyst on the anterior neck in young women: A case report  

Kim YH, Lee J

4488  Extremely rare case of successful treatment of metastatic ovarian undifferentiated carcinoma with high-dose combination cytotoxic chemotherapy: A case report  

Kim HB, Lee HJ, Hong R, Park SG
Acute amnesia during pregnancy due to bilateral fornix infarction: A case report
Cho MJ, Shin DI, Han MK, Yum KS

Ascaris-mimicking common bile duct stone: A case report
Choi SY, Jo HE, Lee YN, Lee JE, Lee MH, Lim S, Yi BH

Eight-year follow-up of locally advanced lymphoepithelioma-like carcinoma at upper urinary tract: A case report
Yang CH, Weng WC, Lin YS, Huang LH, Lu CH, Hsu CY, Ou YC, Tung MC

Spontaneous resolution of idiopathic intestinal obstruction after pneumonia: A case report
Zhang BQ, Dai XY, Ye QY, Chang L, Wang ZW, Li XQ, Li YN

Successful pregnancy after protective hemodialysis for chronic kidney disease: A case report
Wang ML, He YD, Yang HX, Chen Q

Rapid remission of refractory synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome in response to the Janus kinase inhibitor tofacitinib: A case report
Li B, Li GW, Xue L, Chen YY

Percutaneous fixation of neonatal humeral physeal fracture: A case report and review of the literature
Tan W, Wang FH, Yao JH, Wu WP, Li YB, Ji YL, Qian YP

Severe fundus lesions induced by ocular jellyfish stings: A case report
Zheng XY, Cheng DJ, Lian LH, Zhang RT, Yu XY

Application of ozonated water for treatment of gastro-thoracic fistula after comprehensive esophageal squamous cell carcinoma therapy: A case report
Wu DD, Hao KN, Chen XJ, Li XM, He XF

Germinomas of the basal ganglia and thalamus: Four case reports
Huang ZC, Dong Q, Song EP, Chen ZJ, Zhang JH, Hou B, Lu ZQ, Qin F

Gastrointestinal bleeding caused by jejunal angiosarcoma: A case report
Hui YY, Zhu LP, Yang B, Zhang ZY, Zhang YJ, Chen X, Wang BM

High expression of squamous cell carcinoma antigen in poorly differentiated adenocarcinoma of the stomach: A case report
Wang L, Huang L, Xi L, Zhang SC, Zhang JX

Therapy-related acute promyelocytic leukemia with FMS-like tyrosine kinase 3-internal tandem duplication mutation in solitary bone plasmacytoma: A case report
Hong LL, Sheng XF, Zhuang HF

Metastasis of esophageal squamous cell carcinoma to the thyroid gland with widespread nodal involvement: A case report
Zhang X, Gu X, Li JG, Hu XJ
<table>
<thead>
<tr>
<th>Page No.</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>4595</td>
<td>Severe hyperlipemia-induced pseudoerythrocytosis - Implication for misdiagnosis and blood transfusion: A case report and literature review</td>
<td>Zhao XC, Ju B, Wei N, Ding J, Meng FJ, Zhao HG</td>
</tr>
<tr>
<td>4603</td>
<td>Novel brachytherapy drainage tube loaded with double 125I strands for hilar cholangiocarcinoma: A case report</td>
<td>Lei QY, Jiao DC, Han XW</td>
</tr>
<tr>
<td>4615</td>
<td>Primary hepatic myelolipoma: A case report and review of the literature</td>
<td>Li KY, Wei AL, Li A</td>
</tr>
<tr>
<td>4624</td>
<td>Endoscopic palliative resection of a giant 26-cm esophageal tumor: A case report</td>
<td>Li Y, Guo LJ, Ma YC, Ye LS, Hu B</td>
</tr>
<tr>
<td>4633</td>
<td>Solitary hepatic lymphangioma mimicking liver malignancy: A case report and literature review</td>
<td>Long X, Zhang L, Cheng Q, Chen Q, Chen XP</td>
</tr>
<tr>
<td>4644</td>
<td>Intraosseous venous malformation of the maxilla after enucleation of a hemophilic pseudotumor: A case report</td>
<td>Cai X, Yu JJ, Tian H, Shan ZF, Liu XY, Jia J</td>
</tr>
<tr>
<td>4660</td>
<td>Bochdalek hernia masquerading as severe acute pancreatitis during the third trimester of pregnancy: A case report</td>
<td>Zou YZ, Yang JP, Zhou XJ, Li K, Li XM, Song CH</td>
</tr>
<tr>
<td>4667</td>
<td>Localized primary gastric amyloidosis: Three case reports</td>
<td>Liu XM, Di LJ, Zhu JX, Wu XL, Li HP, Wu HC, Tuo BG</td>
</tr>
<tr>
<td>4676</td>
<td>Displacement of peritoneal end of a shunt tube to pleural cavity: A case report</td>
<td>Liu J, Guo M</td>
</tr>
<tr>
<td>4681</td>
<td>Parathyroid adenoma combined with a rib tumor as the primary disease: A case report</td>
<td>Han L, Zhu XF</td>
</tr>
</tbody>
</table>
ABOUT COVER

Peer-reviewer of World Journal of Clinical Cases, Prof. Adrián Ángel Inchauspe, obtained his MD in 1986 from La Plata National University (Argentina), where he remained as Professor of Surgery. Study abroad, at the Aachen and Tubingen Universities in Germany in 1991, led to his certification in laparoscopic surgery, and at the Louis Pasteur University in Strasbourg France, led to his being awarded the Argentine National Invention Award in 1998 for his graduate work in tele-surgery. He currently serves as teacher in the Argentine Acupuncture Society, as Invited Foreigner Professor at the China National Academy of Sciences and Hainan Medical University, and as editorial member and reviewer for many internationally renowned journals. (L-Editor: Filipodia)

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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

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Intraosseous venous malformation of the maxilla after enucleation of a hemophilic pseudotumor: A case report

Xu Cai, Jian-Jun Yu, Hao Tian, Zhen-Feng Shan, Xiao-Yu Liu, Jun Jia

CASE REPORT

Intraosseous venous malformation of the maxilla after enucleation of a hemophilic pseudotumor: A case report

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Abstract

BACKGROUND
Hemophilic pseudotumor (HP) is a rare complication in patients with hemophilia. The lesion most frequently occurs in the long bones, pelvis, small bones of the hands and feet, or rarely in the maxillofacial region. Postoperative changes in HP are seldom arrested, whereas angiogenesis characterized by disturbed wound healing in HP may cause vascular malformations.

CASE SUMMARY
We report the case of an 11-year-old boy who was affected by maxillary intraosseous venous malformation. Enucleation of an HP without factor replacement was performed initially on the right side of the maxilla 3 years ago. The patient was referred to us because of painless swelling in the same location. Factor replacement and subtotal maxillectomy were performed. Pathological examinations revealed intraosseous venous malformation.

CONCLUSION
This study is the first to document the development of intraosseous venous malformation after enucleation of an HP in the maxillofacial region. Angiogenesis characterized by disturbed wound healing in patients with hemophilia may be pivotal in the pathogenesis of this condition.
Hemophilia A and B are uncommon X-linked recessive disorders that almost exclusively affect male individuals. A common complication, often following trauma, is bleeding in joints, muscles, and bones. Repeated intramuscular or intraosseous hemorrhage rarely results in an expanding lytic lesion termed “hemophilic pseudotumor (HP)”. In osseous tissues, HP commonly occurs in long bones, pelvis, and small bones of the hands and feet.

Starker[1] first described the morbid anatomy of two subperiosteal hematomas in a patient with hemophilia. HP usually manifests as chronic, encapsulated slow-growing hematomas resulting from recurrent hemorrhages. In the jaws, occlusal trauma caused by unilateral chewing habits in patients with hemophilia increases the prevalence of HP in severe and mild conditions.

Postoperative changes in HP are rarely arrested, whereas angiogenesis characterized by disturbed wound healing may cause vascular malformations. Coagulation abnormalities affect vasculogenesis and angiogenesis. A population-based case-control study has revealed that coagulation abnormalities are biological risk factors for severe cardiovascular malformations, and this finding is supported by clinical evidence and recent advances in vascular biology[2]. In hemophilic arthropathy, Bhat et al[3] found soft-tissue hyperproliferation with marked induction of neoangiogenesis and evolving abnormal vascular architecture in FVIII-deficient mice. This case report describes an 11-year-old male patient who suffered from venous malformation (VM) of the maxilla after he underwent enucleation of an HP.

**CASE PRESENTATION**

**Chief complaints**
An 11-year-old boy was admitted to Head and Neck Surgery Department with a major complaint of painless swelling of the right facial region.

**History of present illness**
The patient’s symptoms started 6 mo ago, and he was referred to us for a painless swelling in the right maxillary region that gradually enlarged for 6 mo.

**History of past illness**
In 2011 in Hunan province, China, the patient was subjected to enucleation of the same region without factor replacement. The lesion was first diagnosed as a simple bone cyst, and the pathology consultation finally diagnosed it as a hemophilic pseudotumor of the right maxilla.
Physical examination
The face of the patient was symmetrical (Figure 1A). The partially enlarged right maxilla was palpated in intraoral physical examination. The upper right side of the vestibular groove was shoaled (Figure 1B).

Laboratory examinations
Preoperative examination revealed a coagulation disorder diagnosed as hemophilia A (factor VIII, 23% of normal activity).

Imaging examinations
CT displayed a multicystic low-density mass measuring 3 cm × 2.5 cm × 2.5 cm in the right maxilla. The body of the right maxilla manifested irregular swelling (Figure 2A). The lesion occupied the right maxillary sinus. A molar was squeezed into the right maxillary sinus and embedded in the superior part of the lesion close to the canalis opticus (Figure 2B).

Preoperative diagnosis
Odontogenic tumor of the maxilla

Histopathology and immunohistochemical findings
The specimens were retrieved from the Department of Pathology, The Second Xiangya Hospital of Central South University. In the lesion of the first surgery, no signs of epithelium were found, although a fibrous tissue lining was observed. In the wall of the lesion of the first surgery, remote hemorrhage and clot organization were obvious, which is different from simple bone cyst (Figure 3A). Abundant intracellular and extracellular hemosiderin deposition was noted (Figure 3B). Histological characteristics are necessary to rule out other entities that cause unilocular radiolucent jaw lesions. Combined with coagulation function results in this case, the multicystic radiolucent lesion in the maxilla was confirmed to be an HP.

The postoperative pathological results of the second surgery verified the diagnosis of intraosseous VM of the right maxilla. Histomorphology and immunohistochemistry results revealed that the lesions were abundant in vessels positive for CD31, a marker of endothelial components, and negative for GLUT-1, which is strongly expressed by endothelial cells of infantile hemangiomas at all stages of their evolution and is not expressed by other benign vascular anomalies and reactive proliferations (Figure 4A and B). The lesions were diagnosed as intraosseous venous malformation according to the ISSVA classification. Venous malformations are most common in slow-flow vascular malformations that commonly form in the oral maxillofacial region. Angiogenesis characterized by normal pericyte coverage in patients with hemophilia has been reported in hemophilic arthropathy[4]. Moreover, the increased vascular density likely caused the formation of vascular anomalies.

FINAL DIAGNOSIS
The final diagnosis of the presented case was intraosseous venous malformation of the maxilla.

TREATMENT
Cryoprecipitate was given preoperatively to correct coagulation disorders. Then, the patient underwent right subtotal maxillectomy. A nasal lateral and nasolabial sulcus incision was made. The complete resection of the lesion of the maxilla and removal of contents of the maxillary sinus and ethmoidal cellules were then performed, and the pavimentum orbitae and zygomatic process of the maxilla were preserved (Figure 5B).

OUTCOME AND FOLLOW-UP
Iodoform gauze was placed in the right maxillary sinus and wound, and drainage was performed through the inferior nasal channel in the first week. The patient had an uneventful postoperative clinical course. Factor VIII was given per 8 h after surgery for
Figure 1 Physical examination of the maxillofacial region. A: The face was symmetrical; B: The upper right side of the vestibular groove was shoaled.

3 d. The faciomaxillary region was supported by the residual bone and the face was almost symmetrical (Figure 5A). The pathological result indicated intra-maxillary venous malformation. No evidence of recurrence was found during the routine 5-year follow-up.

DISCUSSION

The pathogenesis of HP is poorly understood. In this case, the critical factors probably included hemorrhagic tendency, occlusal trauma, oppressive bone resorption, tooth germ development, and angiogenesis. Intraosseous hemorrhage, caused by unilateral chewing and following unconscious occlusal trauma, might be implicated in the origin and progression of this condition into remote hemorrhage and clot organization. Pathological results revealed that the multicystic bone cyst was covered with a thin layer of connective tissue without epithelial components. Remote hemorrhage and organization were found in the wall. Abundant intracellular and extracellular hemosiderin deposition was noted, which is similar to electron micrograph showing a deposit of electron-dense hemosiderin granules surrounded by bands of fibrous collagen in the study by Fernandez de Valderrama et al. Similar to a simple bone cyst, the wall without epithelial components was pathologically interesting. Thus, this condition was easily misdiagnosed as simple bone cyst, with the consideration of hemosiderin deposition caused by enucleation. In simple bone cysts, materials for histological examination may be difficult to obtain because the soft tissue lining of the bony cavity may be entirely absent or thin. These materials usually consist of loose fibrovascular tissues with signs of previous hemorrhage, such as cholesterol clefts and macrophages loaded with iron pigment. Incidentally, threadlike calcification can be observed. In some instances, simple bone cysts may occur simultaneously with various fibro-osseous lesions, but the possibility of pseudocystic stromal degeneration in an ossifying fibroma cannot be ruled out for certain. After the mass was subjected to enucleation, replacement therapy, which is important in sequential therapy for bony remodeling, was not performed. Hoffman et al. found that cutaneous wounds heal more slowly in hemophilic mice than in wild-type mice. Hemophilic mice also exhibit
Cai X et al. Maxillary intraosseous venous malformation

Figure 2  Computed tomography scan and 3D reconstruction displayed a multicystic low-density shadow in the right maxilla. A: The body of the right maxilla manifested irregular swelling; B: The orange arrow shows a molar that was squeezed into the right maxillary sinus and embedded in the superior part of the lesion close to the canalis opticus.

Figure 3  Microscopic examination with haematoxylin and eosin staining was performed. A: No signs of epithelium were found, although a fibrous tissue lining was observed; B: Remote hemorrhage and clot organization supported the diagnosis of hemophilic pseudotumor (magnification, × 100).

histological abnormalities even after their skin defect is closed. Hemophilic wounds are characterized by reduced inflammatory cell influx and increased angiogenesis. The radiological appearance of multicystic bone cysts may be related to occlusal trauma in the periapical region and tooth germ development, which are common in odontogenic cysts. In the patient’s dentition developmental period, tooth displacement was associated with the compression of the lesion between deciduous dentition and permanent dentition. Consequently, the second molar was pushed into the maxillary sinus. After 3 years, the second molar was pushed into the anterior superior part of the right maxillary sinus close to the optic canal. The loose maxillary structure may also participate in lesion progression.

Increased angiogenesis characterized by normal pericyte coverage in patients with hemophilia has been observed in hemophilic arthropathy. Zetterberg et al[4] investigated whether angiogenesis is disturbed in hemophilic arthropathies and found
Figure 4 Immunohistochemical findings of the lesion of the second surgery. A: Immunohistochemistry results revealed that the lesions of the second surgery were abundant in the vessels positive for CD31, a marker of endothelial components; B: The vessel endothelium of the lesions was negative for GLUT-1 (magnification, × 200).

Figure 5 Physical examination of the maxillofacial region half a month after surgery. A: The faciomaxillary region was supported by the residual bone and the face was almost symmetrical; B: Computed tomography scan and 3D reconstruction displayed complete resection of the lesion of the maxilla and removal of the contents of the maxillary sinus and ethmoidal cells. The pavimentum orbitae and zygomatic process of the maxilla were retained.

that microvascular density and VEGF expression are increased. Acharya et al\(^8\) examined the potential role of neoangiogenesis in the pathogenesis of hemophilic arthropathies. The sera from patients with hemophilia elicit an angiogenic response in endothelial cells, but this response is abolished by blocking VEGF. In our patient, venous malformation occurred after the enucleation was completed. Therefore, neoangiogenesis may play a role in its pathogenesis. For further evidence, several resected specimens from the second surgery were retrieved from the Department of Oral Pathology, Stomatology School of Wuhan University, and the components of the vascular structure were confirmed by detecting the CD31 and Glut-1 expression levels. The representative immunohistochemical results are shown in Figure 4A and B. Compared with the specimens from the first surgery, the lesions from the second surgery contained numerous CD-31-positive vessels, which were negatively stained.
Described by Lazarovits et al. in 1968, the first report of HP in the maxillofacial region involved an 11-year-old patient with mild hemophilia and with a major complaint of gum bleeding and mass swelling in the left mandible. The present study reports the case of an 11-year-old male child who suffered from intraosseous VM of the maxilla after he underwent enucleation of an HP. This study is the first to document the development of intraosseous VM of the maxilla after HP surgery. Nevertheless, several sporadic cases of HP in the maxilla have been reported. We review the treatments for HP in the maxilla in the literature (Table 1)\[10-14\]. All of the patients are male and young. Five cases of HP in the maxilla have been published. In 2004, Steele et al.\[15\] presented a case of HP in the paranasal sinus. We present an unusual case involving an 11-year-old male patient who suffered from intraosseous VM of the maxilla after he received enucleation of an HP. We provided insights into the possible link between hemophilia and vascular anomalies. Thus, further studies should be performed to determine whether hemophilia-related wound healing can cause vascular anomalies.

CONCLUSION

We herein describe the unusual case of 11-year-old male patient who suffered VM of the maxilla after enucleation of an HP, and meanwhile provide some underlying clues for the possible link between HP and VM development. Therefore, we emphasize that long-term routine follow-up after HP enucleation is necessary, and the up-regulated angiogenesis in patients with hemophilia should not be overlooked, especially in oral and facial regions.
Table 1 Reported cases of pseudotumor of hemophilia of the maxilla

<table>
<thead>
<tr>
<th>No.</th>
<th>Ref.</th>
<th>Year</th>
<th>Age (yr)</th>
<th>Type</th>
<th>Severity</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Marquez et al</td>
<td>1982</td>
<td>13</td>
<td>A</td>
<td>Moderate</td>
<td>Hemimandibular resection, conservative treatment</td>
<td>5 yr: No recurrence</td>
</tr>
<tr>
<td>2</td>
<td>De Sousa et al</td>
<td>1995</td>
<td>11</td>
<td>A</td>
<td>Severe</td>
<td>Curettage</td>
<td>1 yr: No recurrence</td>
</tr>
<tr>
<td>3</td>
<td>Zheng et al</td>
<td>1997</td>
<td>13</td>
<td>A</td>
<td>Mild</td>
<td>Curettage</td>
<td>Not discussed</td>
</tr>
<tr>
<td>4</td>
<td>Lima et al</td>
<td>2008</td>
<td>12</td>
<td>A</td>
<td>Mild</td>
<td>Enucleation/EACA, FR</td>
<td>9 mo: No recurrence</td>
</tr>
<tr>
<td>5</td>
<td>Hu et al</td>
<td>2010</td>
<td>11</td>
<td>A</td>
<td>Mild</td>
<td>Radiotherapy, enucleation, FR</td>
<td>10 yr: No recurrence</td>
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<tr>
<td>6</td>
<td>The present case</td>
<td>2011</td>
<td>9</td>
<td>A</td>
<td>Mild</td>
<td>Enucleation</td>
<td>2 yr: Development of venous malformation</td>
</tr>
</tbody>
</table>

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