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Case Report

Radicular Cyst with Associated Extramedullary Hematopoiesis: A Previously Undescribed Phenomenon. Literature Review and Report of a Case

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Abstract

Objectives: The aim of this paper is to present the first case of a radicular cyst, with associated extramedullary hematopoiesis in a 57- year- old male patient. Prompted by this unique finding, we reviewed the existing literature systematically to identify extramedullary hematopoiesis in the maxillofacial area.

Study Design: A review of the evidence was conducted using PubMed/MEDLINE and Google Scholar. The following key words were applied: "extramedullary hematopoiesis" OR "extramedullary haematopoiesis" AND "maxillofacial", OR "jaw", OR "sinonasal tract", OR "paranasal sinus", OR "sinus".

Results: The electronic search revealed 23 published cases; all relevant reported parameters were listed in tabular form. All cases were associated with a hematological disease, which is in contrast to our case. 11 years of follow up care revealed no systemic hematologic disorder. In view of this main difference, our case is the first described radicular cyst with extramedullary hematopoiesis. Histologic illustrations are presented, hematopoietic cells including erythrocytes, myeloid cells and megakaryocytes were characterized according to their lineage by immunohistochemistry.

Conclusion: Extramedullary hematopoiesis in the maxillofacial area can be found in patients without underlying hematologic disease. Each radicular cyst should be examined histopathologically, due to the possibility of unexpected morphological findings.

Keywords: Extramedullary Hematopoiesis; Radicular Cyst; Immunohistochemistry; Mandible

Introduction

Radicular cysts represent the most frequent odontogenic cysts in the jaw, independent of the patient's ethnic origin or geographical location [1]. Because of their etiology they are ranked in the inflammatory subtypes of odontogenic cystic lesions [2]. The highest incidence occurs in the anterior maxilla with the lateral incisors most frequently involved [3,4]. Gender appears to play no role in affected patients. Although radicular cysts emerge at any age, most cases appear between the ages of 20 and 40 [5]. Histologically, radicular cysts present with a capsule-like fibrous tissue and they are partially or totally lined by a non-keratinized stratified squamous epithelium. Inflammation often goes along with the extension of

arcading or net-like epithelial formations into the capsule. Furthermore, cholesterol deposits, foreign body giant cells, hemosiderin granules and foamy cells can be found. Also well-known is the rare occurrence of mucous cells, ciliated cells, or Rushton bodies [4,6]. There have been reports of cases with exceptional histologic findings, instead of as sebaceous glands [7], squamous odontogenic tumor-like proliferation [8], *in situ* or invasive squamous cell carcinoma [9,10], focal intramural giant cell lesions [11], tooth structure components [12], or unusual radiological appearances such as multilocularity [13].

We however, demonstrate the first case of a radicular cyst with associated extramedullary hematopoiesis (EMH) located in the lower jaw of a 57-year-old male. In addition, we present a systematic review of the literature on EMH in the maxillofacial area.

Material and Methods

The literature was reviewed using PubMed and Google Scholar for publications related to EMH in the maxillofacial area in the English language. The literature review without restriction of publication year was carried out on July 31, 2020.

The following key words were applied: (extramedullary hematopoiesis OR extramedullary haematopoiesis) AND (maxillofacial OR jaw OR mandibular OR sinonasal tract OR paranasal sinus OR sinus). Inclusion criteria were retrospective studies, case series, and case reports of extramedullary hematopoiesis in the maxillofacial area. Exclusion criteria were reviews, articles in languages other than English, conference abstracts, and studies with unavailable full texts. Additionally, the references of all publications were cross-checked for reports on extramedullary hematopoiesis in the maxillofacial area not found before by using the above- mentioned strings. However, no further cases were found.

The following data were extracted from the articles included in the review: author and year of publication, patients, gender and age, anatomical location, histopathological features and associated hematological disorder.

Results

Review of the literature

Over the years, there have been a number of case reports. As it is seen in table 1, the search revealed 23 published cases, instead of ; which 18 were males (age range 2.33 - 78 years, mean 27.6 years) and 5 were females (age range 13 - 71 years, mean 45 years).

19 cases of EMH occurred in the sphenoid, ethmoid or maxillary sinus, one case in the meatus superior, one in the lacrimal fossae and nasolacrimal ducts and one case of EMH was located in the tongue (Table 1). All cases were associated with a hematological disease including β - thalassemia, sickle cell disease, myelofibrosis, myelodysplastic syndrome, myeloproliferative neoplasm, chronic myelomonocytic leukemia, idiopathic autoimmune thrombocytopenia or multiple myeloma (Table 1). 9 cases provided appropriate histological illustration of EMH, using hematoxylin and eosin-staining. Only one out of 23 cases used immunohistochemical examination (Table 1).

Case Report

A 57-year-old male patient reported to the Department of Maxillofacial Surgery, at the Medical University of Graz with two lesions in the jaw. Additional preoperative imaging by CT-scan revealed two different sized radiolucent cystic lesions. The smaller one was located in the region 36 and with a diameter of 1 cm, whereas the larger one was situated in 46-47 with a diameter of 2 cm (Figure 1). A surgical removal of both lesions was performed under local anesthesia, and the operative specimens were submitted for histopathological examination.

Pathological examination

Microscopically, both cysts were lined by a non-keratinizing squamous epithelium resting on a fibrous capsule. The capsule of the smaller cyst revealed a partial thickening. Hemosiderin granules where near the lumen, and at the periphery a denser connective tissue with cholesterol clefts, accompanying foreign body giant

Authors	Sex	Age	Anatomical location	Associated haematological disorder	Histopathological features
Andreou., *et a*l. 1984	m	10	maxillary sinus	β- thalassaemia	no
Fernandez., *et al*. 1995	m	2,3	maxillary sinus	sickle cell disease	no
Joseph., *et al*. 2000	m	18	sphenoid sinus	β- thalassaemia/sickle cell disease	no
Vargas., *et al*. 2001	f	71	left nasal cavity/left maxillary sinus	myelofibrosis	yes/H&E
Reed Kearney and Nasser 2002	m	24	maxillary sinus/right sphenoidal sinus	β- thalassemia major	yes/H&E
Rizzo., *et al*. 2003	f	68	left ethmoid and sphenoidal sinus	myelofibrosis/ Paget disease	no
Brennan., *et al*. 2004	m	72	right nose/meatus superior	MDS/MPN/CMML	yes/H&E, IHC
Collins., *et al*. 2005	m	13	maxillary and ethmoid sinus	sickle cell disease	no
Baskurt., *et al*. 2006	m	60	lacrimal fossae/nasolacrimal ductus	MPD/myelofibrosis	yes/H&E
Ittipunkul., *et al*. 2007	f	13	ethmoid and sphenoid sinus	β- thalassemia/Hb E disease	no
Santonja., *et al*. 2007	m	78	tongue	multiple myeloma	yes/H&E
Kulendra., *et al*. 2009	f	32	sphenoid sinus	β- thalassaemia/sickle cell disease	no
Stamataki., *et al*. 2009	m	12	left maxillary sinus	sickle cell disease	yes/H&E
Bizzoni., *et al*. 2010 Case 1	m	30	right maxillary sinus/nasal fossa	idiopathic autoimmune thrombocytopenia	yes/H&E
Case 2	m	29	left ethmoid sinus/nasal fossa	intermediate β-thalassemia	yes/H&E
Hoskins Dorton and Mims 2011	f	41	right nasal cavity/ maxillary sinus	β-thalassemia	no
Sklar., *et al*. 2013	m	14	sphenoid sinus	sickle cell disease	yes/H&E
Özgür., *et al*. 2014	m	10	maxillary sinus/sphenoid sinus	sickle cell disease	no
Reiersen., *et al*. 2014	m	4	maxillary sinus	sickle cell disease	no
Vanikieti., *et al*. 2016	m	18	sphenoid sinus	β- thalassemia/Hb E disease	no
Caiado., *et al*. 2017	m	75	right maxillary sinus	Myelofibrosis CAHA	no
Densky., *et al*. 2018	m	11	right sphenoid sinus	hereditary spherocytosis	no
Clark., *et al*. 2020	M	17	left maxillary sinus	sick cell disease	Yes/H&E

Table 1

m: Male, f: Female, H&E: Hematoxylin and Eosin-staining IHC: Immunohistochemistry, MDS: Myelodysplastic Syndrome MPN: Myeloproliferative Neoplasia, CMML: Chronic Myelomonocytic Leukemia, CAHA: Chronic Autoimmune Hemolytic Anemia Hb: Hemoglobin

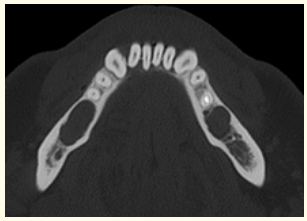

Figure 1: CT-scan revealed two different sized radiolucent cystic lesions. The smaller one was located in the region 36 and with a diameter of 1 cm, whereas the larger one was situated in 46-47 with a diameter of 2 cm. Thinning of the mandibular cortex is seen, cortical border is still defined as a thin rim.

cells. Closely attached to this capsular area were an abundance of hematopoietic cells with intermingled lipocyte elements (Figure 2). The hematopoiesis consisted of cells from the myelopoiesis, erythropoiesis and megakaryopoiesis. This was additionally supplemented by lymphoid cells, which were sometimes arranged in follicular structures with formation of germinal centers. For further characterization of the hematopoietic cells immunohistochemistry was performed according to their lineage. Thus, nucleated erythrocytic cells and erythrocytes were identified with an antibody to Glycophorin C (Figure 3). The application of an antibody to myeloperoxidase (MPO) indicated myeloid cells (Figure 4). An antibody to CD42b highlighted the presence megakaryocytes (Figure 5). 11 years of follow up care revealed no systemic hematologic disease.

Figure 2: High power view of the extramedullar hematopoesis demonstrates cells of all hematopoetic lineages.

Figure 3: Nucleated erythropoetic cells and erythrocytes are demonstrated by an antibody to Glycophorin C.

Figure 4: Myeloid cells are highlighted by an antibody to myeloperoxidase.

Figure 5: Megakaryocytes are highlighted with an antibody to CD 42b.

Discussion

The combined occurrence of a radicular jaw cyst and an EMH is extraordinary in a twofold respect. First, although radicular jaw cysts are very frequent [1], only a limited number of major deviations from the classical histopathological features are known. How-

23

Flow Chart

ever, such a lesion with an associated EMH has never been reported. Second, EMH in the maxillofacial area has been described several times [14-35], but never in combination with a radicular jaw cyst. In the 23 above stated reports, only 10 cases proved EMH as illustrated by hematoxylin and eosin- stained sections, however rather superficially. Only one case showed illustration with immunohistochemistry. This is in contrast to our report, which documents the EMH photographically in detail, especially the immunohistochemical characterization of cells of all hematopoietic lineages.

It is accepted that inflammation is a trigger in the formation of radicular cysts [2]. However, the etiology and mechanism of an EMH is far more complicated. In general, this condition arises more often in association with hematologic diseases both benign or malignant [36,37]. It could also be found in patients with non-hematological malignancies [38], or in tissues with non-malignant changes and without associated hematologic disorder as in the uterus [39-41] or skin [42,43].

The etiology of EMH in our case example is very interesting. In Table 1, all patients with EMH in the maxillofacial area suffered from a hematologic disease, in contrast to our case example in which no disorder was present. Therefore, the radicular cyst itself

must cause the formation of an EMH. This may be explained by the fact that the cyst developed along with previous inflammation and hemorrhage. This was then followed by scaring granulation tissue, which could be proven microscopically. Also, the surrounding mandibular bone may play at least some role. In this context it is remarkable, that foci of EMH have been found in patients without any underlying hematologic disease. Cases include the uterus in a degenerated leiomyoma [39], chronic endometritis [40], endometrial polyps with osseous metaplasia [41], as well as in the skin in pilomatricomas [42] and a trichilemmal cyst [43]. All these lesions have inflammatory changes and sometimes lipocyte elements in common with our case study. Some of them display additionally marked degeneration and osseous metaplasia.

It is evident that associated reactive changes represent a substantial factor in patients with non-diseased bone marrow inflammation. Therefore, it can be considered the cause of EMH.

Special cells like mesenchymal stromal cells, vascular cells, perivascular cells, macrophages and endosteal cells are an important indicator when looking for EMH. These have been found to be important elements in the formation of hematopoietic stem cells niches. These elements, which are already seen in the inflammatory process, are considered to play a major role in the mainly chemokine-driven mechanism of EMH [36].

Conclusion

The present study reported a radicular cyst with associated EMH in a male patient. Based on the reviewed literature, this is the first described case. EMH in the maxillofacial area can be found in patients without underlying hematologic disease. Each radicular cyst should be examined histopathologically, due to the possibility of unexpected morphological findings.

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