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Case Report

Germinal Center- Like Diffuse Large B cell Lymphoma of the Frontal Sinus Misdiagnosed as a Pott's Puffy Tumor

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Abstract

Non-Hodgkin's Lymphoma (NHL) of the frontal sinus is very rare and early diagnosis is usually made with some delay because of the non-specificity of the clinical presentation and overlapping with other diseases. We report herein the story of a 40-year-old man who presented to the outpatient clinic with pain and swelling of the forehead. The first diagnosis was a sub-acute rhinosinusitis mimicking a Pott's puffy tumor. On the CT scan, there was a partial opacity of the left frontal sinus with osteomyelitis of the anterior and posterior tables of the frontal sinuses. He received broad-spectrum antibiotics and systemic glucocorticosteroids. He responded well to the treatment but the symptoms and signs relapsed at the completion of the treatment.

A second CT scan was performed but no significant improvement was found compared with the first CT scan. As there was no pus coming from the middle meatus we decided to take specimen for bacteriological and histopathological examination during a therapeutic window. This was done via a supraciliary incision and frontal trephine. The final diagnosis was a diffuse large B cell lymphoma, germinal center B cell like subtype. He underwent 6 cycles of chemoimmunotherapy with R-CHOP and central nervous system prophyllaxis via intrathecal methotrexate. 2 years after the initiation of the treatment the patient is still free of symptom and disease confirmed by serial PET scans.

Keywords: B Cell Lymphoma; DLBCL; Frontal Sinus; GCB; NHLs; Pott's Puffy Tumor; Swelling of the Forehead

Introduction

Malignancies of the paranasal sinuses are commonly of epithelial origin. The most frequent are squamous cell carcinoma, adenocarcinoma and adenoid cystic carcinoma [1]. Malignant lymphomas are the most common non-epithelial head and neck malignancies. They are divided into Hodgkin's disease and Non-Hodgkin's Lymphomas (NHLs). The majority of NHLs are of B-cell subtypes in European countries and North America [2-4]. Primary Paranasal Sinus Lymphomas (PPSL) are rare. The most common type of lymphoma is the diffuse large B cell lymphoma followed by follicular lymphoma, Peripheral T Cell Lymphoma (PTCL), T/NK nasal type, Burkitt lymphoma and others [4-12]. The median age at presentation is the sixth decade. (Range: 27-97 years).

The maxillary sinus is by far the most commonly involved, followed by the ethmoid sinus and the nasal cavity [4-12]. The clinical presentation of PPSL is nonspecific at the early stage and can be misconfused with other "benign" diseases leading to a protracted time between the onset of the disease, its dignosis and the initiation of the treatment [9-11]. We report herein a unique case of a Diffuse Large B-Cell lymphoma, germinal center B cell subtype, of the frontal sinus misdiagnosed with a Pott's puffy tumor. We report the medical history, the imaging, the modality of treatment and review the pertinent literature.

Clinical Case

A 40-year-old man presented to the outpatient clinic with 4 weeks history of pain and forehead swelling, which was smooth with no tenderness. The medical history was unremarkable except a story of previous "rhinosinusitis". There was no sign of fever, nocturnal sweating or body weight loss. On examination, he had a 2 cm non-tendersoft tissue swelling on themedianside of his forehead (Figure 1a and 1b). The sensitivity in the frontal region was preserved. There was no lymphadenopathy. Anteriorrhinoscopy and nasal fiberoscopy were normal with no purulent discharge coming from the middle meatus. Initial Computed Tomography (CT) scan of the paranasal sinuses revealed a central opacity of the left frontal sinus with a subcutaneous soft tissue swelling and lytic bone changes compatible with osteomyelitis in the anterior and posterior tables of the frontal bone.

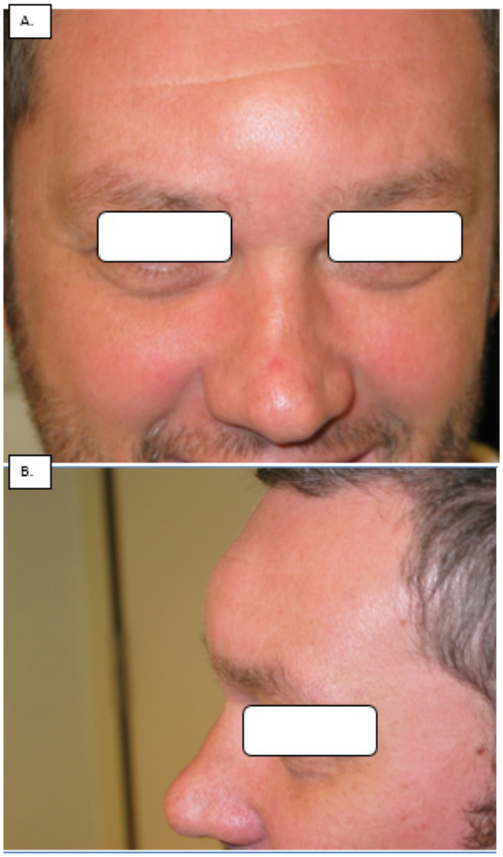

Figure 1: visualization of the swelling of the forehead without any inflammatory sign.

The other paranasal sinus cavities were free of disease (Figure 2a-d). A presumptive diagnosis of Pott's puffy tumorwas made. Broad-spectrumantibiotics and systemic steroids were administrated. The patient responded well to this therapy but the swelling relapsed at the completion of the medical treatment. A second CT scan was then performed. It confirmed the recurrence of the swelling. However, there were no significant changes compared with the first CT scan. Therefore, we decided to do a therapeutic window and to take specimens for histopathological and bacteriological evaluation. This was done under general anesthesia via a supraciliary incision. We associated the biopsies with a trephine of the frontal sinuses. On gross examination, the subcutaneous tissue was edematous and hyperplasic. There were some bony defects in the anterior table of the frontal bone but no pus was found. The culture did not yield any pathogen.

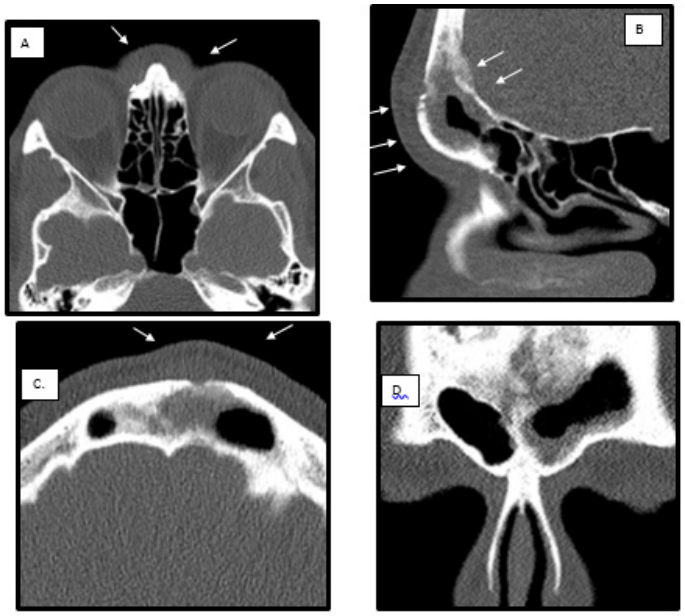

Figure 2: Computed tomography showing on cut A & C a swelling of the forehead and in front of the nasal bones. Cut B shows erea of osteomyelitis in the anterior and posterior walls of the frontal sinus. Cut D shows a partial opacity of the left frontal sinus.

The pathologist used immunohistochemistry staining to make the diagnosis. This one was a diffuse Large B-cell Lymphoma, germinal center B cell like subtype, (GCB) DLBCL (Figure 3a and 3b). The patient was referred to the hematologists for staging and chemotherapy. Whole body Positron Emission Tomography (PET) scan showed a hypermetabolic lesion involving the frontal sinus but no significant lymphadenopathy. Bone marrow aspiration was negative for malignant infiltrate. The disease was classified as stage 1E according to the Ann Arbor Staging system. The patient underwent 6 cycles of chemotherapy with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP), and central nervous system prophylaxis via intrathecal methotrexate. He did not receive radiotherapy. 24 months after completion of therapy, he is still free of disease based on serial positron emission tomography and computed tomography scanning.

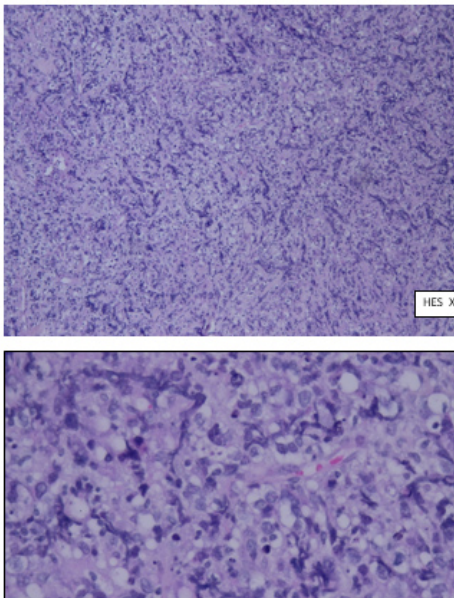

Figure 3A: Diffuse large B-cell lymphoma. .The tumor exhibited a diffuse and polymorphic proliferation of large lymphoid cells with vesicular and irregular nuclei containing central or membrane-bound nucleoli. There are numerous apoptotic bodies .Hematoxylin and eosin stain: X10 & X 40.

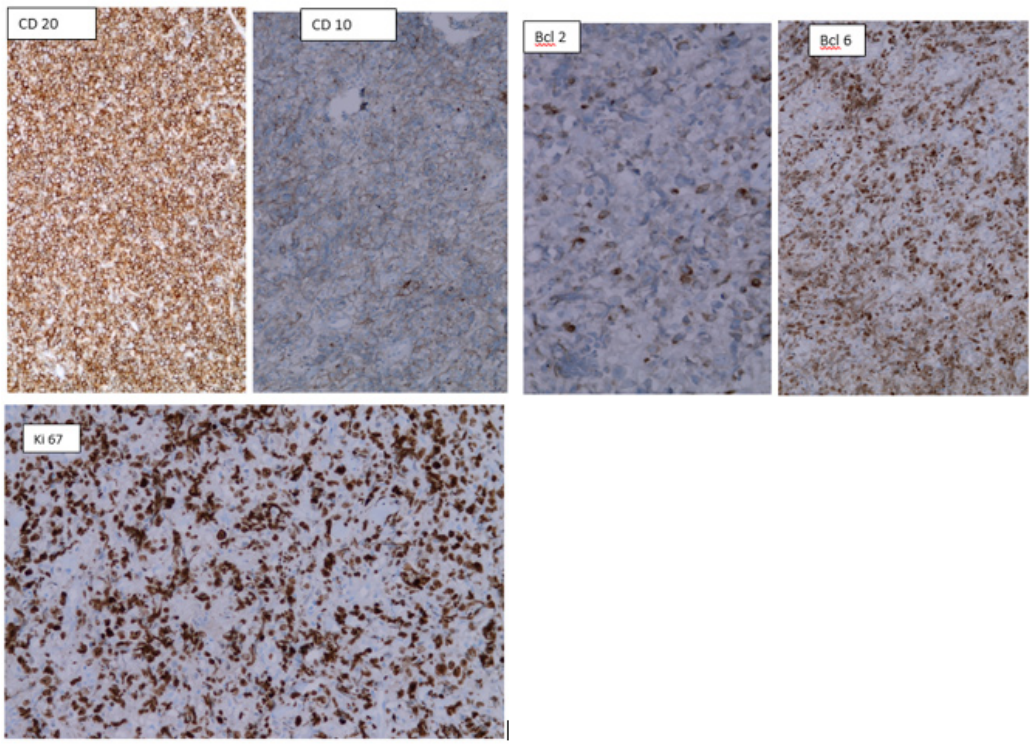

Figure 3B: Immunohistochemistry: B. Immunohistochemistry demonstrated positivity of the tumor cells for CD20, CD10 and Bcl6. The Ki-67 proliferation index was high.

Discussion

This case illustrates perfectly well the difficulty to make thecorrect diagnosis in case of a swelling of the forehead. This is explained by the fact that the clinical presentation overlaps with many other diseases such as hematoma or abscess of the forehead, Pott's puffy tumor, frontal mucocele, osteoma, fibrous dysplasia, primary sinus malignancies or metastasis to the frontal sinus (from primary sites: kidney, prostate, lung, breast..). Clinical examination particularly the tumor consistency can give some information to orientate the diagnosis but this is highly subjective. Therefore, imaging remains the additional investigation to make the differential diagnosis. In the present case, 2 diagnoses were specifically considered: a Pott's puffy tumor and an expanding process of the frontal sinus.

Pott' Puffy Tumor (PPT) is a rare but serious clinical entity seen as a complication of an acute or subacutefrontal sinusitis [13-17]. It is described as a subperiosteal or subgaleal abscess in the frontal bone secondary to frontal osteomyelitis. The swelling concerns the forehead or the scalp. It is usually well circumscribed, overlying the area of frontal osteomyelitis. Fever, headache, frontal sinus tenderness, nasal discharge and in some cases nausea, vomiting and photophobia can be present. PPT can be complicated by preseptal and orbital cellulitis and intracranial infection (with venous thrombosis, epidural abscess, subdural empyema, and brain abscess). PPT is mostly found in adolescents but may occur in adults [15, 16]. PPT must be treated promptly with broad-spectrum antibiotics for 4 to 6 weeks. Surgical intervention is necessary for removal of osteomyelitic bone.

In the present case, the first diagnosis of PPT was wrong. Even if the patient responded well to antibiotics and mostly to the systemic steroids the swelling of the forehead relapsed at the completion ofthe treatment. Therefore, a revision of the diagnosis was required and led to the definitive diagnosis of a diffuse large B cell lymphoma germinal center like subtype, of the frontal sinus. Non-Hodgkin's Lymphomas (NHL) involving the paranasal sinuses are rare. Primary involvement of the frontal sinus is exceptional with less than 20 cases published in the worldwide literature. This represents only 0.17%-1. 63% of all lymphomas [18, 19]. Table 1 summarizes some case reports published in the worldwide literature. There are also some cases included in case series [3, 9-11]. This disease affects mostly the middle aged and the elderly (40-80 yrs) patient with a slight male predominance. Our patient was a 40-year-old man. However,one case has been reported in the pediatric population [20].

Author	year	Patient/Age yo	Signs	Treatment	Follow-up
[20]	2019	M/11	Orbital /sinus/antcranialfossa	DLBC Frontal sinus Cranialisation Orbital and skull bas Reconstruction CTx	Free of disease at 12 months
[21]	1984	F/43	Frontal headache/persistent nasal drainage/ Frontal sinus & Intracranial extension	DLBCL Frontal sinus obliteration CTx (CHOP)	Free of disease at 20months
[22]	2000	M/58	T diagnosis: acute rhinosinusitis with orbital cellullits/medica treat FES/ relapse:biops1sMedial canthus edema & erythema, frontal headaches, rhinorrhea, PND, epistaxis, nasal obstruction, hyposmia	B CELL NHL (high grade) I E CTx (CHOP) CNS prophylaxis Sinus surgery	Free of diseaseat 3months
[23]	2004	M/83	Pain, nasal discharge, headache, nasal bleeding	III E DLBCL CTx (CHOP) RTx	NA
[4]	2005	M/43	Frontal headache, frontal buldging involving the upper eyelidpain/orbit	DLBCL High grade Steroids RXT	Death at 1month
[24]	2005	M/84	Orbital invasion	DLBC Steroids RXt	Death at 9 months
[25]	2007	M/55	Osteomyelitis frontal sinus	II E External frontotomy / chiomio/radiot/CNS prophyllaxis	Free of disease at 18 months
[26]	2015	M/ 69	History of sinusitis/2 previous endoscopic surgeries	DLBC/Pott's puffy Craniotomy/ CHimiot/RXT	Free of disease at3 years
[27]	2011	M/42	Frontal sinus and cranial nerve palsy	IV E R-CHOP CNS prophyllaxis RXT	Free of disease at 50months

[28]	2012	F/ 61	Pott's:osteomyelitis Unilat frontal lymphoma	DLBC / frontal trephine CTx	Free of disease at at 12 months
[18]	2018	M/67	Orbital extension /diplopia/ frontal sinus	DLBC / II E CTx immunotherapy	Free of disease at at 12 months
Eloy	2020	M/40	Frontal lump/Pott' spuffy tumour	DLBCL: R-CHOP CNS prophyllaxis	Free of disease at 24months

Table 1: DLBCL: Diffuse Large B Cell Lymphoma/; CNS prophyllaxis: Central Nervous System prophyllaxis with metothrexate/; RXT: Radiotherapy /CTx: Chimiotherapy usually R-CHOP/yo: Years.

Symptoms and signs are vague and non-specific particularly at the early stage of the disease. Actually, the patient may report nasal obstruction, nosebleeds, rhinorrhea, post nasal dripping, frontal pressure, headache, fever, weight loss and nocturnal sweating. In later stage he may present with a swelling of the forehead, exophthalmos, diplopia, meningitis, neuralgia and cranial nerve palsies [18-26]. Moreover, it is not so rare that the patient reports a story of "rhinosinusitis". In our case the initial diagnosis was a Pott's puffy tumour. This error has also been published by el Hakim, Nemet, Chain, Khan and Wong [22, 24, 25, 26, 28]. This rhinosinusitis usually responds well to the medical treatment particularly to systemic steroids leaving the clinician with a false sense of security and delayingin diagnosis and treatment. The patient could even have undergone FESS before the definitive diagnosis was made [8].

In 2012, Yen et al published a series of 32 patients who presented with a paranasalsinus lymphoma. In 20 patients (62.5%), the first impression was benign or malignant nasal neoplasm, but in the other 12 patients (37.5%) the first diagnosis was a rhinitis or rhinosinusitis [29]. Imaging of the paranasal sinuses is mandatory to assess a sinus disease. In case of lymphoma of the frontal sinus a variety of images can be found: partial or complete opacity of the frontal sinuses, signs of osteomyelitis of the anterior and posterior walls of the frontal sinus with osteolytic bone, and in later stages orbital or intracranial extension. The definitive diagnosis is based on histology. Large specimens are required and must be taken as soon as possible. In our case the final diagnosis was A Diffuse Large B Cell Lymphoma (DLBCL), germinal center like B cell subtype. DLBCL is the most common type of NHLs in Western countries. It represents a heterogeneous group of diseases [30-32].

There are different classifications. WHO classifications are certainly the references; There are different editions published in 2001, 2008 and 2016. However, these classifications are very large and complex. In 2016, a classification was published on the basis of GEP (gene expression profiles) studies [32]. These studies propose a molecular classification of DLBCL. Actually they are 3 main subtypes of DLBC; Germinal Center B Cell (GCB), Activated B Cell (ABC) and Primary Mediastinal B-Cell Lymphoma (PMBLCL). These subtypes arise from different stages of B-cell differentiation. They are associated with distinct genetic abnormalities and different oncologic outcomes. GCB-DLBC has a better response to Chemoimmunotherapy (CI) compared to patients with ABC-DLBCL. Because GEP studies need substantial time, technological expertise and resources, pathologists prefer to use IHC (immunohistochemistry) staining method performed on Tissue Microarrays (TMAs).

Several algorithms and methods have been published by (Hans[32], Muris[33], Choi[34] and Tally to categorize DLCL cases as GCB like or non-GCB- like DLBCL Hans' algorithm utilizing staining for CD20, CD10, Bcl-6 and Mum1 was used for this clinical case [32-34]. Leading to the definitive diagnosis of a germinal center B cell lymphoma also called as GCB-like B-cell lymphoma. The prognostic depends on the histological subtype of lymphoma but also of the staging [35-37];

According to the Ann Arbor classification, our patient was on stage1E as the tumor was localized in the frontal sinuses without any lymphadenopathy or intracerebral extension. NHL scan be managed by Chemotherapy (CHOP), immunotherapy, radiation therapy, and surgery in various combinations. Lymphomas are chemosensitive and radiosensitive pathologies. Adjunction of rituximab has dramatically improved the response to the chemotherapy [38, 39]. Because the lymphomas involving the paranasal sinus have a high propensity for CNS dissemination our patient received R-CHOP associated to injection of intrathecal methotrexate [40].

Surgery has limited indications. The role of surgery is primarily diagnostic [3]. The goal is to obtain specimen for histological evaluation. In our case it consists of performing biopsies only. In the literature extensive surgery has been done such as maxillectomy or cranialisation of the frontal sinus because the diagnosis was done at later stage.

Survival of paranasal non-Hodgkin lymphoma is not so poor if diagnosed early in the course of the disease. The 5- and

10- year disease-free survival rates range both between 50% and 60%, respectively [37,38]. After 2 years follow up our patient is still symptom free and free of disease. Longer follow up remains necessary for the 3 upcoming years.

Conclusion

Sinonasal NHLs of the paranasal sinuses are rare. Frontal localization is exceptional. Because of this rarity and the non-specificity of the symptoms and signs at the early stages of the disease, the diagnosis may take some time and can be misconfused with other diseases such as Pott's puffy tumour. Histological evaluation is necessary. Chemoimmunotherapy (R-CHOP) is the treatment of choice associated to CNS prophyllaxis with methotrexate. Large surgery may be necessary in very advanced cases.

Inform Consent

The patient agrees for the publication of his clinical story.

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