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## Contents

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### REVIEW

- 1499** Review of the risk factors for SARS-CoV-2 transmission  
*Li X, Xia WY, Jiang F, Liu DY, Lei SQ, Xia ZY, Wu QP*

### MINIREVIEWS

- 1513** Regulation of the expression of proinflammatory cytokines induced by SARS-CoV-2  
*Zhang XN, Wu LJ, Kong X, Zheng BY, Zhang Z, He ZW*

### ORIGINAL ARTICLE

#### Case Control Study

- 1524** Efficacy and safety of short duration radiotherapy combined with chemotherapy for advanced rectal cancer  
*Gao SQ, Zhang YC, Zhang C, Wang SJ, Ren W, Yuan N, Wen JY*

#### Retrospective Study

- 1532** Effects of transjugular intrahepatic portosystemic shunt using the Viatorr stent on hepatic reserve function in patients with cirrhosis  
*Yao X, Zhou H, Huang S, Tang SH, Qin JP*
- 1543** Primary and secondary postoperative hemorrhage in pediatric tonsillectomy  
*Xu B, Jin HY, Wu K, Chen C, Li L, Zhang Y, Gu WZ, Chen C*
- 1554** Dynamic monitoring of serum liver function indexes in patients with COVID-19  
*Lin H, Wu LJ, Guo SQ, Chen RL, Fan JR, Ke B, Pan ZQ*
- 1563** Construction of a clinical survival prognostic model for middle-aged and elderly patients with stage III rectal adenocarcinoma  
*Liu H, Li Y, Qu YD, Zhao JJ, Zheng ZW, Jiao XL, Zhang J*
- 1580** Short-term outcomes of radiofrequency ablation for hepatocellular carcinoma using cone-beam computed tomography for planning and image guidance  
*Yao XS, Yan D, Jiang XX, Li X, Zeng HY, Li H*
- 1592** Intra-arterial thrombolysis for early hepatic artery thrombosis after liver transplantation  
*Li T, Sun XD, Yu Y, Lv GY*
- 1600** Study on pathogenic genes of dwarfism disease by next-generation sequencing  
*Yang LL, Liang SS*

- 1610** Effects of cooperative nursing and patient education on postoperative infection and self-efficacy in gastrointestinal tumors

*Qiao L, Zeng SQ, Zhang N*

### Observational Study

- 1619** Elevated soluble 4-1BB is associated with serum markers of hepatitis B virus in patients with chronic hepatitis B

*Zhan MR, Gao XZ, Wang C, Peng F, Wang XM, Xu HQ, Niu JQ*

### CASE REPORT

- 1631** Balloon-assisted endoscopic submucosal dissection for treating small intestinal lipomas: Report of two cases

*Chen HY, Ning SB, Yin X, Li BR, Zhang J, Jin XW, Sun T, Xia ZB, Zhang XP*

- 1639** Dysphagia in a patient with ankylosing spondylitis: A case report

*Wang XW, Zhang WZ*

- 1646** Autologous scalp skin grafting to treat toxic epidermal necrolysis in a patient with a large skin injury: A case report

*Xue DD, Zhou L, Yang Y, Ma SY*

- 1654** Epstein-Barr virus-positive diffuse large B-cell lymphoma with human immunodeficiency virus mimicking complicated frontal sinusitis: A case report

*Yoon S, Ryu KH, Baek HJ, An HJ, Joo YH*

- 1661** Multiple well-differentiated retroperitoneal liposarcomas with different patterns of appearance on computed tomography: A case report

*Xie TH, Ren XX, Fu Y, Ha SN, Liu LT, Jin XS*

- 1668** Sarcomatoid carcinoma of the prostate with bladder invasion shortly after androgen deprivation: Two case reports

*Wei W, Li QG, Long X, Hu GH, He HJ, Huang YB, Yi XL*

- 1676** Metastatic thymic-enteric adenocarcinoma responding to chemoradiation plus anti-angiogenic therapy: A case report

*Li M, Pu XY, Dong LH, Chang PY*

- 1682** Solid pseudopapillary neoplasm-diagnostic approach and post-surgical follow up: Three case reports and review of literature

*Abudalou M, Vega EA, Dhingra R, Holzwanger E, Krishnan S, Kondratiev S, Niakosari A, Conrad C, Stallwood CG*

- 1696** Vancomycin-induced thrombocytopenia in endocarditis: A case report and review of literature

*Guleng SR, Wu RH, Guo XB*

- 1705** Human menstrual blood-derived stem cells as immunoregulatory therapy in COVID-19: A case report and review of the literature

*Lu J, Xie ZY, Zhu DH, Li LJ*

- 1714** Pure transvaginal natural orifice transluminal endoscopic surgery right hemicolectomy for colon cancer: A case report  
*Song ZJ, Shi YQ, Jiang YM, Liu K, Li Y, Wang CG, Zhao R*
- 1720** Hyperglycemic hemianopia: A case report  
*Xiang XH, Fang JJ, Yang M, Zhao GH*
- 1728** Mucinous appendiceal neoplasm: A case report  
*Chirca A, Negreanu L, Iliesiu A, Costea R*
- 1734** Reconstructing abdominal wall defects with a free composite tissue flap: A case report  
*Wang J*
- 1741** Mononeuropathy multiplex associated with systemic vasculitis: A case report  
*Chae HJ, Kim JW, Lee YL, Park JH, Lee SY*
- 1748** Congenital fiber-type disproportion presenting with type II respiratory failure after delivery: A case report  
*Yang HM, Guo JX, Yang YM*
- 1755** Use of three dimensional-printing in the management of floating aortic thrombus due to occult aortic dissection: A case report  
*Wang TH, Zhao JC, Xiong F, Yang Y*

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## Epstein-Barr virus-positive diffuse large B-cell lymphoma with human immunodeficiency virus mimicking complicated frontal sinusitis: A case report

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### Abstract

#### BACKGROUND

Primary non-Hodgkin's lymphoma of the frontal sinus is extremely rare. In addition, Epstein-Barr virus (EBV) has been reported to play a role in the development of human immunodeficiency virus (HIV)-related malignant lymphomas. To the best of our knowledge, there is no report for the HIV-associated, EBV-positive primary diffuse large B-cell lymphoma (DLBCL) in the frontal sinus.

#### CASE SUMMARY

We present a unique case of HIV-associated, EBV-positive DLBCL in the frontal sinus in a 46-year-old man. Computed tomography of paranasal sinuses revealed dense opacification of the right frontal sinus with combined soft tissue swelling. Based on the clinical and radiological findings, the initial diagnosis was



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complicated frontal sinusitis, presenting Pott's puffy tumor. Unexpectedly, HIV testing was positive on preoperative laboratory test, and the frontal sinus lesion was confirmed as EBV-positive DLBCL on biopsy.

## CONCLUSION

Through this article, we suggest that EBV-positive DLBCL should be considered as possible diagnosis for patients with nonspecific space-occupying lesion of the paranasal sinuses. We also highlight an importance of clinical suspicion in diagnosing HIV infection because HIV serology is not routinely tested in patients with paranasal sinus problem.

**Key Words:** Lymphoma; Paranasal sinus; Human immunodeficiency virus; Epstein-Barr virus; Computed tomography; Case report

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**Core Tip:** Primary diffuse large B-cell lymphoma in the frontal sinus is extremely rare. It can mimic complicated sinusitis and may be easily overlooked at the initial diagnostic workflow in the clinical practice. When we meet the frontal sinus opacification with combined overlying soft tissue swelling, it is important for the radiologists and clinicians to include the following disease entity in the differential diagnosis based on imaging findings; complicated sinusitis (Pott's puffy tumor), unilateral non-Hodgkin's lymphoma and destructive metastasis. Awareness and clinical suspicion of this disease are necessary for making an accurate diagnosis and appropriate treatment, particularly in patients with a history of sinusitis which does not response to medical treatment, or in human immunodeficiency virus-positive patients.

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## INTRODUCTION

Primary non-Hodgkin's lymphoma (NHL) in the nasal cavity and paranasal sinuses is very rare<sup>[1-3]</sup>. Of these, diffuse large B-cell lymphoma (DLBCL) is the most common subtype worldwide; however, to date, only 18 cases of primary DLBCL in the frontal sinus have been reported in the literature<sup>[4-8]</sup>. In addition, malignant lymphomas occur higher rates in patients with human immunodeficiency virus (HIV) infection compared with the general population, and the most common subtype is DLBCL<sup>[9,10]</sup>. Also, Epstein-Barr virus (EBV) has been reported to play a role in the development of HIV-related malignant lymphomas, and has been identified in 30%-90% of DLBCL<sup>[11]</sup>. Although 18 cases of primary DLBCL in the frontal sinus have been reported<sup>[4-8]</sup>, there is no report for the HIV-associated, EBV-positive DLBCL in the frontal sinus with its radiological findings. Herein, we share our experience with a unique case of the HIV-associated, EBV-positive DLBCL in the frontal sinus, mimicking complicated sinusitis because of its atypical imaging feature in immunocompromised patient. We also highlight the importance of clinical suspicion in diagnosing HIV-associated lymphoma in patients with a paranasal sinus problem.

## CASE PRESENTATION

### Chief complaints

A 44-year-old male presented with the right forehead pain.

### **History of present illness**

He had right forehead pain for 1 mo, and soft tissue swelling in the right forehead and right ptosis for 2 wk.

### **History of past illness**

His medical history was unremarkable and there was no history of fever and palpable cervical lymphadenopathy, but he described mild weight loss and fatigue.

### **Personal and family history**

The patient's personal and family history was unremarkable.

### **Physical examination**

Physical examination revealed hard, immobile, tender mass on his right forehead.

### **Laboratory examinations**

His laboratory findings showed increased erythrocyte sedimentation rate (ESR, 108 mm/h; normal range, 0-9 mm/h) and C-reactive protein (CRP, 7.4 mg/L; normal range 0.0-5.0 mg/L) with mild anemia and slightly decreased count of white blood cell.

### **Imaging examinations**

Computed tomography (CT) of paranasal sinuses was performed and the images revealed dense opacification of the right frontal sinus with combined soft tissue swelling (Figure 1A-C). There was minimal bony erosion in the anterior wall of the right frontal sinus without enhancing solid component. Based on the clinical and radiological findings, the initial diagnosis was complicated frontal sinusitis, presenting Pott's puffy tumor.

### **Preoperative laboratory examination**

On preoperative laboratory tests, we found that his HIV testing was positive. HIV-1 RNA quantification (real-time polymerase chain reaction) revealed HIV-1 RNA was  $3.31 \times 10^5$  copies/mL (normal range < 20) and  $5.627 \times 10^5$  IU/mL (normal range < 34). Lymphocyte subset test showed CD4 13.2%, CD3 84.3%, CD8 66.4% with white blood cell  $3.44 \times 10^3/\mu\text{L}$ , and lymphocyte 32.3%. His CD4 lymphocyte count was 147 cells/ $\mu\text{L}$ . Antiretroviral therapy was initiated with a combination of tenofovir alafenamide, elvitegravir, emtricitabine and cobicistat. Co-trimoxazole and acyclovir were administered for prophylaxis of opportunistic infections.

### **Biopsy result**

Then, biopsy was performed by endoscopic sinus surgery under general anesthesia to rule out malignant tumor. The histopathological examination showed an infiltrate of large atypical lymphocytes associated with necrosis, and admixed small lymphocyte. Immunohistochemical staining results showed large atypical lymphoid cells expressing CD20, BCL-2 (90%), CD79a, Ki-67 (80%) and MUM-1 (35%) (Figure 2). ALK1, BCL-6, CD3, CD5, CD10, CD15, CD30, CD56, CD138, Granzyme B, PAS and GMS were negative. *In situ* hybridization for EBV was positive, and the result of polymerase chain reaction test for EBV was also positive in the specimen, showing  $1.70 \times 10^4$  copies/mL. Finally, the lesion was confirmed as EBV-positive DLBCL.

### **Imaging examination (F-18 fluorodeoxyglucose positron emission tomography/CT) for staging**

Additional F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT was performed for evaluating initial stage, and the lesions showed high FDG uptake with maximum standardized uptake value of 14.4 g/mL (Figure 1D). There was no significant hypermetabolic lesion to suggest lymphoma involvement beneath the diaphragm on F-18 FDG PET/CT. He was at stage II according to the Ann Arbor staging system, and international prognostic index was 1 point.

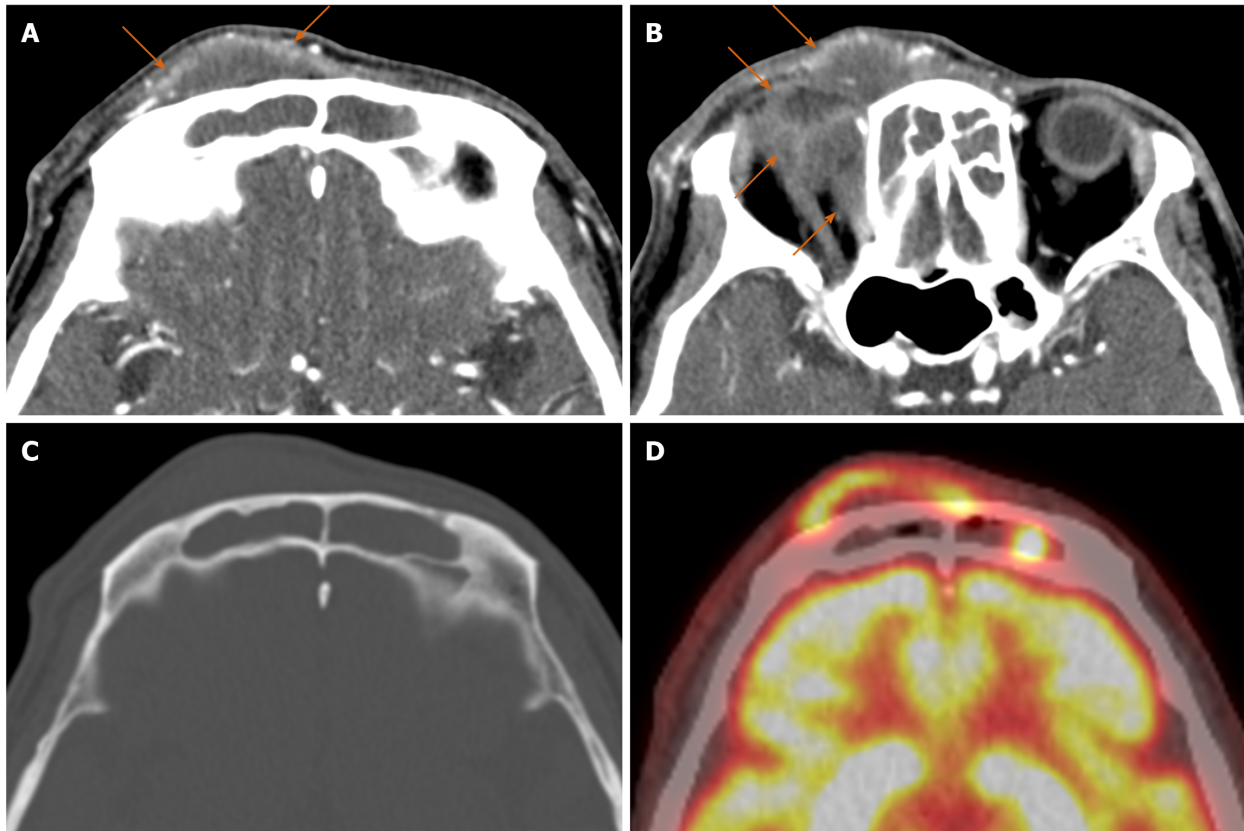
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## **FINAL DIAGNOSIS**

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EBV-positive DLBCL in frontal sinus.





**Figure 1** A 46-year-old male presented with the right forehead pain. A and B: Axial contrast enhanced paranasal sinus computed tomography (CT) shows fluid-like opacification in both frontal sinuses with combined soft tissue lesion in the right forehead and medial portion of the right orbit. There is mild marginal enhancement around the soft tissue lesion without enhancing solid component; C: There is no definite bone erosion in the anterior wall of the right frontal sinus; D: F-18 fluorodeoxyglucose (FDG) positron emission tomography/CT shows irregularly increased FDG uptake with maximum standardized uptake value of 14.4 g/mL in the marginal portion of the right forehead lesion which corresponds to marginal enhancement on paranasal CT.

## TREATMENT

The patient underwent chemotherapy for treatment of DLBCL.

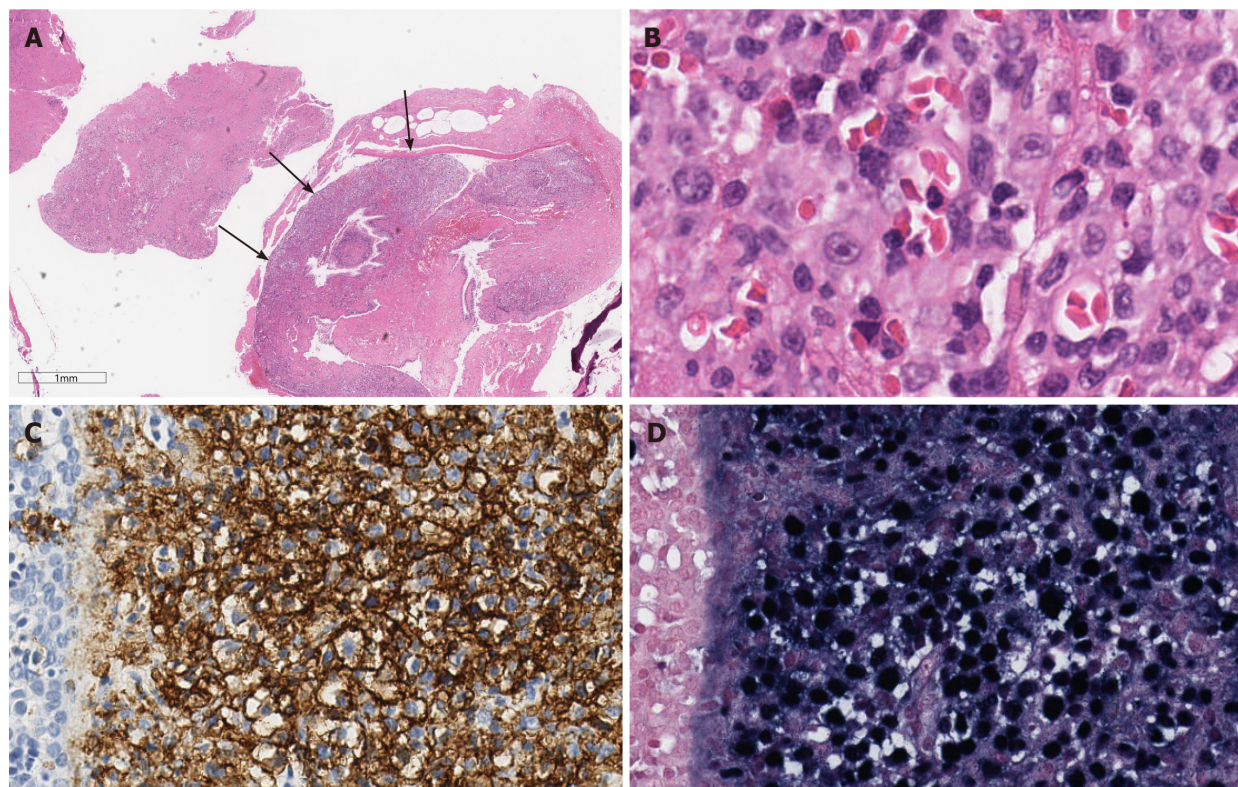
## OUTCOME AND FOLLOW-UP

About 4 mo after the diagnosis of EBV-positive DLBCL, the patient passed away in 2 wk of chemotherapy from pneumonia and sepsis by cytomegalovirus infection.

## DISCUSSION

Primary malignancies in the frontal sinus are rare, reportedly accounting for about 1.0% of sinonasal malignancies<sup>[12]</sup>. In the previous study<sup>[12]</sup>, squamous cell neoplasm was the most common histologic subtype (39.8%), followed by NHL (18.7%), epithelial neoplasm not otherwise specified (10.5%) and adenocarcinoma (9.9%). Manifestations of frontal sinus malignancies are often nonspecific, thus leading to a misdiagnosis for benign diseases such as sinusitis, mucocele, or osteomyelitis. It is known that the overall prognosis for patients with frontal sinus malignancies was poor, with a 5-year survival rate of 31%-50%<sup>[13]</sup>.

Of the primary sinonasal malignancies, NHL is rare, estimated to be between 0.2% and 2.0% of all NHLs<sup>[1,2]</sup>. Most of them occur in the maxillary sinuses, followed by the ethmoid sinuses and the nasal cavity. NHL in frontal sinus is an extremely rare condition<sup>[3]</sup>. DLBCL is the most common subtype of NHL worldwide, generally representing 30%-40% of all cases in different geographic regions<sup>[8]</sup>. To date, only 18 cases of primary DLBCL in the frontal sinus have been reported in the existing



**Figure 2 Histopathologic features of the patient's tumor.** A: Tissue from the sinonasal cavity is mostly composed of necrotic abscess, except for the hypercellular tumorous area (arrows) surrounding the respiratory epithelium; B: On higher magnification, the large tumor cells show immunoblastic morphology with amphophilic cytoplasm and single prominent nucleoli (inset); C: Positive CD20 immunostaining highlights neoplastic large B cells, suggestive of diffuse large B-cell lymphoma; D: The tumor cells are diffusely positive for Epstein-Barr virus *in situ* hybridization.

English-language literature<sup>[4-7]</sup>. Therefore, knowledge of the frontal sinus DLBCL is limited.

Diagnosis of paranasal lymphoma is usually delayed in daily practice because the early stage is often asymptomatic or nonspecific, and a complete investigation is postponed until the tumor mass produces obvious symptoms<sup>[14]</sup>. The previous studies demonstrated that clinical manifestation of DLBCL in the frontal sinus were common symptoms owing to the direct effect of tumor mass such as frontal headache, facial swelling, nasal discharge or nasal obstruction<sup>[4-7]</sup>. In the previous studies, imaging findings showed nonspecific opacification of the involved sinus with or without expansion or enhancement. In the current case, CT images demonstrated dense opacification of the right frontal sinus with minimal bony erosion and combined overlying soft tissue swelling, but with no definitely enhancing component. These findings were common radiological features of complicated sinusitis, therefore, not leading to a diagnosis of malignant lymphoma. In addition to CT findings, increased ESR and CRP of serum inflammatory markers made the diagnosis more indicative of nontumorous inflammatory conditions in our case.

In addition, it is well-known that HIV-infected patients have higher rates of malignant lymphomas compared with the general population, and DLBCL is the most common subtype of lymphoma in HIV patients<sup>[9,10]</sup>. HIV contributes to lymphomagenesis by several different mechanisms as follows: genetic alterations, induction of chronic B-cell activation by immune dysfunction, and loss of immunoregulatory control of oncogenic herpesviruses like EBV and Kaposi sarcoma-associated herpesvirus<sup>[15]</sup>. In addition, EBV, also known as human herpesvirus 4, is one of the most common human viruses, with about 95% of the world's population showing an asymptomatic life-long carrier status. EBV infects memory B cells, which are the EBV reservoir in healthy individuals, and the disruption of this regulated balance between virus and host immune system can result in EBV-associated B cell lymphoproliferation<sup>[16]</sup>. In HIV patients, EBV has been reported to play a role in the development of HIV-related malignant lymphomas which has been identified in 30%-90% of DLBCL<sup>[11,17-19]</sup>. On imaging study, most EBV-related lymphomas show atypical image features including propensity for extranodal involvement and extensive tumor

necrosis<sup>[20]</sup>. Therefore, EBV-related sinonasal lymphoma is more difficult to diagnose on imaging study owing to its atypical imaging features as in this case, compared to typical lymphoma that exhibit homogeneous nature. In the present case, we found that HIV testing was positive on preoperative laboratory tests before the endoscopic sinus biopsy. In addition to clinical rarity of the primary frontal sinus DLBCL, our case suggests that clinical suspicion is the most important for diagnosing HIV-associated, EBV-positive DLBCL because HIV serology is not routinely tested in patients with paranasal sinus problem.

## CONCLUSION

DLBCL is very rare but can occur in the frontal sinus. Like the present case, it can mimic complicated sinusitis and may be easily overlooked at the initial diagnostic workflow in the clinical practice. When we meet the frontal sinus opacification with combined overlying soft tissue swelling, it is important for the radiologists and clinicians to include the following disease entity in the differential diagnosis based on imaging findings; complicated sinusitis (Pott's puffy tumor), unilateral NHL and destructive metastasis. Awareness and clinical suspicion of this disease are necessary for making an accurate diagnosis and appropriate treatment, particularly in patients with a history of sinusitis which does not respond to medical treatment, or in HIV-positive patients.

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