



The Trend of Changes in Paranasal CT Scan in Patients with Hematologic Malignancy Under Chemotherapy

Shervin Shokouhi ^{1,2}, Ilad Alavi Darazam ^{1,2}, Shiva Shabani ^{1,2,*}, Dina Jalalvand ³, Reyhaneh Family³ and Latif Gachkar^{1,2}

¹Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

²Department of Infectious Diseases and Tropical Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

³Department of Radiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

*Corresponding author: Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: drshivashabani@gmail.com

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Abstract

Objectives: The aim of this study was to evaluate the clinical significance of early screening of computerized tomography scan of paranasal sinuses (PNS CT) in hematologic malignancies before chemotherapy and evaluation of changes after chemotherapy and during neutropenia.

Methods: All 40 new cases of hematologic malignancies with febrile neutropenia in a teaching referral hospital between 2018 and 2019 were enrolled in this study. All of these patients underwent paranasal sinus (PNS) CT scan before chemotherapy, along with other preliminary investigations. Symptoms and signs indicating the infectious process were meticulously followed and monitored before and during chemotherapy as well as the occurrence of febrile neutropenia. All patients were clinically and radiologically evaluated regarding the presumptive diagnosis of invasive fungal sinusitis during prolonged febrile neutropenia (more than 4 days). PNS CTs before and after chemotherapy of all patients were compared by two radiologists and were evaluated based on histopathologic findings of nasal and or paranasal biopsies.

Results: Around 50% of patients with PNS CT scan abnormality suspected inflammatory process including microbial and fungal sinusitis during prolonged febrile neutropenia (more than 4 days) were confirmed that have had similar involvement before starting chemotherapy and these abnormalities have been stable with no significant changes after chemotherapy. The histopathologic examination of sinuses also showed no evidence of invasive fungal infection by endoscopic biopsy. Therefore, the abnormal findings including mucosal thickening in PNS CT during prolonged febrile neutropenia were not consistent with the confirmed invasive fungal infection. The rate of mortality was 2.5% without association with invasive fungal sinusitis.

Conclusions: A considerable number of patients with underlying hematologic malignancies have paranasal sinus involvement such as mucosal thickening that may be misdiagnosed as invasive fungal sinusitis during the hazardous phase of prolonging febrile neutropenia. Thus, performing PNS CT scan before initiation of chemotherapy even though in asymptomatic patients could be helpful to decrease the number of suspected and probable cases of fungal sinusitis based on abnormal findings in PNS CT scan followed by the number of cases undergoing sinus endoscopic surgery.

Keywords: Invasive Fungal Sinusitis, Hematologic Malignancy, Screen Paranasal CT Scan, Neutropenia

1. Background

Invasive fungal sinusitis is an important clinical concern in patients with hematologic malignancies that can be fatal in case of delayed treatment (1, 2). Thus, empiric therapy in patients with prolonged neutropenic fever is initiated based on CT scan findings and then the definitive diagnosis is made based on pathologic findings and functional endoscopic sinus surgery (FESS) (3-5).

The definitive diagnosis of invasive fungal sinusitis requires sinus surgery, sampling, and histopathologic

and mycological examination. However, most patients with hematologic malignancies and leukemia develop neutropenia, coagulopathies, and thrombocytopenia after chemotherapy. Thus, the invasive interventions such as FESS can be dangerous with several morbidities including bleeding and in some cases is not possible to perform (4). On the other hand, mucosal involvement of the paranasal sinuses (PNS) presented as increased mucosal thickness and secretions inside the sinus cavities is not always due to invasive fungal infections and in many cases, bacterial or

non-bacterial infections and other factors such as allergies are considered (6). Sinus surgery that results in the rejection of invasive fungal infection can complicate the treatment process and lead to increased morbidity and complications.

2. Objectives

Therefore, it seems that early PNS CT screening in patients with hematologic malignancy before chemotherapy and its follow-up and comparison with PNS CTs of these patients in the phase of prolonged neutropenic fever during chemotherapy as well as the evaluation of the initial changes and differences in the comparison of CT scans of the two stages can provide physicians insight regarding patients with blood cancer with prolonged neutropenic fever and mucosal involvement, in whom empiric antifungal therapy and FESS can be delayed.

3. Methods

All the new cases of patients with hematologic malignancy in 2018 - 2019 were enrolled in the study. All the patients underwent PNS CT before the commencement of chemotherapy along with other preliminary investigations. These patients were followed up while receiving chemotherapy.

Patients who entered the neutropenic fever stage included those with a single oral temperature above or equal to 38.3 degrees Celsius, or a 38-degree fever or higher within an hour in the absence of a specific reason.

Neutropenia with absolute neutrophil count (ANC) was lower than 500 neutrophils/mL or ANC lower than 1000, which is expected to reach 500 or less within 48 hours. Diagnostic and therapeutic procedures were performed according to the neutropenic fever protocol. (NCCN guidelines version 1.2019).

Patients whose neutropenic fever lasted more than four days despite the initial treatment, laboratory, and imaging interventions, including PNS CT imaging and empiric antifungal therapy, were started according to the protocol of prolonged neutropenic fever even in cases where PNS CT involvement existed before the initiation of chemotherapy.

The researchers did not interfere with the patients' treatment process and only extracted clinical findings and documentation from laboratory and radiology findings and entered them into separate pre-designed checklists.

The exclusion criteria included patients with fever before commencing chemotherapy, with a history of sinus surgery, with a history of invasive fungal rhinosinusitis,

and patients who were treated with antifungal medications.

PNS CT findings were separately interpreted by two radiologists before and during chemotherapy and their findings were included in the patients' checklists. Then, with the diagnosis of possible invasive fungal infection of the PNS, the patients underwent FESS if they met the criteria. These patients were followed up with respect to findings rejecting or confirming invasive fungal infection during endoscopic sinus examination and histopathological examination of sinus tissue specimens and fungal cultures, afterward the results were analyzed.

Finally, the results of sinus invasive fungal infection were compared with evidence obtained before and during chemotherapy, and the frequency and association of invasive fungal sinus infections with imaging findings were collected and analyzed. Also, in cases where FESS was impossible, mortality, morbidity, or treatment complications were analyzed.

4. Results

Forty new cases of neutropenic fever following chemotherapy whose was recently diagnosed with malignancy were enrolled as follows: 25 patients with acute myeloid leukemia (AML), 7 patients with acute lymphoblastic leukemia (ALL), 3 patients with myelodysplastic syndrome (MDS), 2 patients with chronic lymphocytic leukemia (CLL), 1 patient with multiple myeloma (MM), 1 patient with diffuse large B cell lymphoma (DLBL), and 1 patient with aplastic anemia (AA).

Twenty out of the 40 patients developed a prolonged neutropenic fever following chemotherapy, and the treatment and diagnostic protocol for patients with prolonged neutropenic fever were administered. Of the 40 patients enrolled in the study, 14 (35%) findings matched sinusitis before commencing chemotherapy, including 6 patients with acute myeloid leukemia (AML), 4 patients with acute lymphoblastic leukemia (ALL), 1 patient with myelodysplastic syndrome (MDS), 1 patient with chronic lymphocytic leukemia (CLL), 1 patient with multiple myeloma (MM), and 1 patient with aplastic anemia (AA).

In 50% of the patients (20 out of 40), neutropenic fever following chemotherapy was prolonged. Of these, 10 (50%) patients showed evidence of sinusitis at this stage in PNS CT, including 5 AML, 2 ALL, 1 MDS, 1 MM, and 1 AA.

In 10 patients, a comparative study of PNS CT during prolonged neutropenic fever with PNS CT before chemotherapy (50%) disclosed new changes in PNS CT. Nine of these 10 patients underwent FESS. Patients showed no evidence of invasive fungal infection on endoscopy and sampling. There was also no invasive fungal infection on

pathologic examination. Thus, the findings obtained from PNS CT were not consistent with invasive fungal infection.

The rest of the patients with prolonged neutropenic fever following chemotherapy included three patients with AML with the diagnosis of pneumonia, four patients with AML with fever of unknown origin (FUO), two ALL patients with the diagnosis of pneumonia, and one patient with DLBL FUO. In this study, we had one case of mortality (2.5%). This patient had a definitive diagnosis of aplastic anemia and died with the diagnosis of pneumonia and CRBSI.

All individuals agreed to participate in the study and signed written informed consent. All assessments were performed following the principles of the Declaration of Helsinki.

5. Discussion

According to the results of this study, in 50% of the patients, PNS CT involvement during chemotherapy in the phase of prolonged neutropenic fever was related to prior to chemotherapy and was not new, and there was no evidence of invasive fungal infection on pathologic examination and sinus biopsy.

In a study performed in 2019 at Texas Medical Center on a child with unexplained neutropenic fever, the role of sinus CT scan in the neutropenic FUO screening protocol was investigated and it was observed that many of these children had some degrees of underlying mucosal thickening. In patients with neutropenic FUO where CT scan did not show the involvement of sinuses, antifungal therapy was started although pathologic examination might not show pathologic fungal lesions (7).

In another study in 2015 which was performed in Johns Hopkins among 100 patients with underlying hematologic malignancies who were undergoing bone marrow transplantation, CT scans were obtained before and after bone marrow transplantation, which showed that 33% of the patients had abnormal CT scans. Contrary to previous studies that showed the correlation between the presence of sinus involvement on CT scans and the presence of sinuses after bone marrow transplantation, this study found that neither the presence of sinus involvement nor the severity of involvement before bone marrow transplantation was correlated with the progression of sinusitis after transplantation (8).

In another study in 2011 that was performed in ENT-University Hospital, Medical University Graz, Austria 142 patients were scheduled for a liver transplant. Paranasal sinus (PNS) CT scans were performed for screening of sinusitis, of all patients (n = 142), 50 (35.2%) had normal PNS CT scans and 92 (64.8%) had a pathologically changed PNS CT

scan. Seventy-one out of these 92 (77.2%) patients showed no clinical symptoms of sinusitis and no changes in diagnostic endoscopy, 21 (22.8%) patients had symptoms of sinusitis and diseased PNS CT scans. Since there was a high rate (77.2%) of pathological CT scans without sinus symptoms these findings should be considered as accidental and clinically irrelevant (9).

Paranasal sinus CT scans of 169 renal and 43 hepatic transplant recipients were reviewed in Department of Otolaryngology, Baskent University Faculty of Medicine, Ankara, Turkey. Routine paranasal sinus CT scans are not feasible in patients scheduled for organ transplant according to the high rate of false-positive results; therefore, we did not perform radiological imaging methods in every transplant candidate. This means that our patients might already have maxillary mucosal cysts before transplantation (10).

In our study, due to the limited number of patients and lack of invasive fungal infections in the sinuses of these patients, it was not possible to investigate the association between imaging findings and invasive fungal infections, which would become possible with the increase in the number of neutropenic fever patients and more cases of invasive fungal infection.

On the other hand, this study showed that despite the involvement of sinusitis on PNS CT during chemotherapy leading to empiric antifungal therapy and FESS, invasive fungal sinus infection is not present in many patients and primary PNS CT screening of these patients before chemotherapy demonstrates evidence of sinusitis from the beginning.

In conclusion, due to the lack of new changes in neutropenic fever and PNS CT of these patients during chemotherapy compared to the primary PNS CT, PNS CT screening may provide physicians with guidance about treatment of patients with neutropenic fever and mucosal involvement of the sinuses. These patients should be under precise monitoring and clinical follow-up, and empiric antifungal therapy and FESS should be delayed.

Footnotes

Authors' Contribution: Study concept and design: SS, RJ, LG, and IAD. Analysis and interpretation of data: DJ, SS, and RJ. Critical revision of the manuscript for important intellectual content: SS, SS, RJ, LG, DJ, and IAD.

Conflict of Interests: There is no conflict of interest.

Ethical Approval: All assessments were performed following the principles of the Declaration of Helsinki.

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Informed Consent: All individuals agreed to participate in the study and signed written informed consent.

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