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Nasopharyngeal Carcinoma with Generalized Lymphadenopathy and Hematological Abnormalities Masquerade as Lymphoma: A Case Series of Atypical Presentations and Prognostic Significant

Jeneralize Lenfadenopati ve Hematolojik Anormalliklerle Seyreden Nazofarengeal Karsinomun Lenfomayı Taklit Etmesi: Atipik Sunumlar ve Prognostik Önemi Olan Bir Olgu Serisi

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ABSTRACT

Nasopharyngeal carcinoma (NPC) is a unique type of head and neck squamous cell carcinoma, characterized by distinct etiology, epidemiology, and biological characteristics. Neck swelling is the most common presenting symptom, but generalized lymphadenopathy involving other parts of the body is rarely reported. Severe anemia, leukocytosis, and thrombocytopenia are rare but may occur at an advanced stage. The combination of these atypical presentations leads to the more common diagnosis of lymphoma instead of NPC. In addition, the hematological derangements are indicators of a poor prognosis. The clinician should be aware of these atypical presentations to avoid delays in management and worsening of overall survival.

Keywords: Nasopharyngeal carcinoma, generalized lymphadenopathy, severe anemia, leukocytosis, thrombocytopenia

Öz

Nazofarengeal karsinom (NFK), kendine özgü etiyoloji, epidemiyoloji ve biyolojik özelliklerle karakterize, benzersiz bir baş ve boyun skuamöz hücreli karsinom türüdür. Boyunda şişlik en sık görülen başvuru belirtisidir; ancak vücudun diğer bölgelerini içeren jeneralize lenfadenopati nadiren bildirilmiştir. Şiddetli anemi, lökositoz ve trombositopeni de nadir olmakla birlikte ileri evrede ortaya çıkabilir. Bu atipik klinik bulguların bir arada görülmesi, NFK yerine daha sık görülen bir hastalık olan lenfoma tanısının konulmasına yol açabilmektedir. Ayrıca, hematolojik bozukluklar kötü prognoz göstergeleridir. Klinisyenlerin, tedavide gecikmelerin ve genel sağkalımın kötüleşmesinin önlenmesi için bu atipik bulguların farkında olması gerekmektedir.

Anahtar Sözcükler: Nazofarengeal karsinom, jeneralize lenfadenopati, şiddetli anemi, lökositoz, trombositopeni

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a distinct subtype of head and neck squamous cell carcinoma arising in the nasopharynx. It has distinct etiology, epidemiology, and biological characteristics (1). The World Health Organization has classified it into three histopathological types, namely keratinizing, non-keratinizing, and basaloid squamous cell carcinoma (2). It is a rare tumor globally, accounting for only 0.7% of all cancers diagnosed in 2018, but is relatively common in Asia, as 85% of all cases are from this region, especially in East and Southeast Asia (1,3,4).

Neck swelling is the most common presenting symptom, affecting up to 80% of patients (5,6). In contrast, generalized involvement of the lymph node (LN) in other parts of the body, such as the axilla, inguinal region, mediastinum, and abdomen, is rarely reported. The majority of patients with NPC have normal hematological profiles; however, abnormalities may be observed in patients with advanced-stage disease (7). In addition to the extent of the disease, as defined by the tumor node metastasis staging system, anemia, leukocytosis, thrombocytosis, and thrombocytopenia are found to be additional prognostic indicators of an unfavorable prognosis (7).

The combination of generalized lymphadenopathy, severe anemia, leukocytosis, and thrombocytopenia has led to the more common diagnosis of lymphoma rather than NPC. These atypical presentations of NPC may delay diagnosis and treatment and lead to poor overall survival. We present a case series of advanced NPC (stage 4B) presenting with generalized LN enlargement, severe anemia, leukocytosis, and thrombocytopenia, without an obvious mass in the nasopharynx, masquerading as lymphoma at initial presentation, with 100% mortality within 4 months of diagnosis.

CASE REPORTS

Case 1

A 44-year-old male without underlying medical illness presented with painless bilateral neck swellings for 6 months and bilateral axillary and inguinal swellings for 2 months. It was associated with

loss of appetite, weight loss, intermittent fever, and lethargy. He has had lower back pain for the past month, which has limited his ability to work and perform daily activities. There were no nasal or otological symptoms. A full blood picture obtained at another center showed normochromic, normocytic anemia (hemoglobin: 6.7 g/dL), leukocytosis with neutrophilia (white blood cell count: $30.4 \times 10^9/L$, absolute neutrophil count: $22.1 \times 10^9/L$), and thrombocytopenia (platelet count: $92 \times 10^9/L$). In view of the presentations that were more suggestive of lymphoma, with generalized lymphadenopathy and the presence of B symptoms, computed tomography (CT) scans of the neck, thorax, abdomen, and pelvis were performed for staging. The CT scan showed no enhancing lesion in the nasopharynx, oropharynx, or laryngopharynx (Figure 1A). There were multiple enlarged LNs in the cervical, mediastinal, and abdominal regions (Figures 1B, 1C and 1D). Hepatomegaly with multiple ill-defined hypodense lesions was present, and lytic lesions were present in the lumbar spine. He was admitted to the hematology ward and referred to the otorhinolaryngology (ORL) team for an excisional biopsy to obtain a definitive tissue diagnosis. Upon examination, multiple enlarged LNs were present bilaterally in the neck (Figure 2A) and in the axillary and inguinal regions, and hepatomegaly was noted. No obvious mass at nasopharynx or Fossa of Rosenmüller (FOR) on naso-endoscopy examination (Figure 2B). Other head and neck examinations were unremarkable. An excisional biopsy of the left level V cervical LN was performed. Histopathology examination (HPE) and immunohistochemistry (IHC) studies showed metastatic squamous cell carcinoma but unable to determine the primary site of origin. Bone marrow trephine biopsy also demonstrated metastasis from the primary tumor to the marrow. Pan-endoscopy, esophagoscopy, and biopsy were performed due to the unavailability of magnetic resonance imaging (MRI) or positron emission tomography scans at our center. A biopsy of the left FOR confirmed non-keratinizing NPC. The patient was planned to receive palliative chemotherapy for advanced disease (stage IVB) but had a poor Eastern Cooperative Oncology Group (ECOG) performance status and died 3 months after diagnosis from hospital-acquired pneumonia.

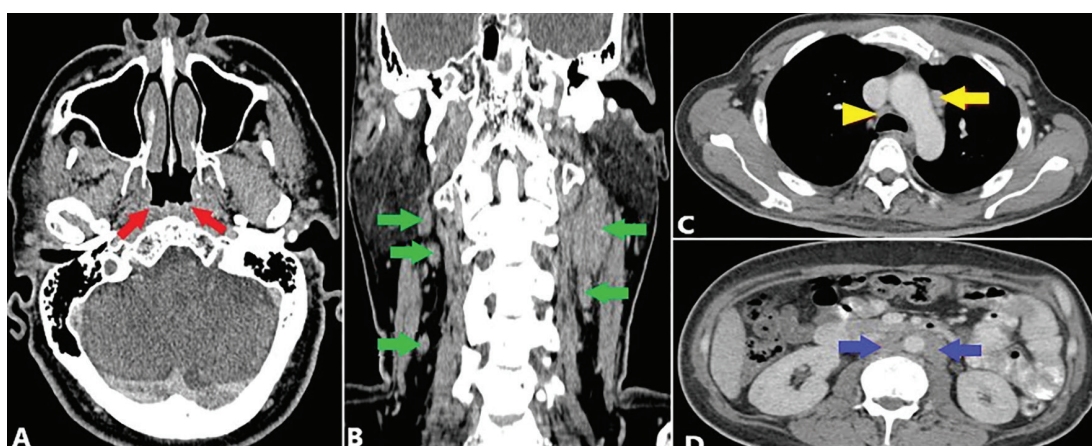


Figure 1. Contrast-enhanced CT scan of neck, thorax, and abdomen. Axial image at the level of the nasopharynx shows no enhancing lesion in the nasopharynx or the FOR (red arrow) (A). Coronal image of the neck shows bilateral cervical nodes at levels II, III, and IV (green arrow; B). An axial thoracic image depicts the right paratracheal LN (yellow arrowhead) and para-aortic LN (yellow arrow) (C). An Axial image of the abdomen shows para-aortic LN enlargement (blue arrow) (D).

CT: Computed tomography, LN: Lymph node, FOR: Fossa of Rosenmüller

Case 2

A 40-year-old man with no underlying medical illness presented with a 3-month history of painless bilateral neck swellings and a 1-month history of bilateral axillary and inguinal swellings. It was associated with symptoms of anemia, loss of appetite and weight loss, intermittent fever, and night sweats for one month. There was no nasal or otological symptoms. The full blood picture showed hypochromic, microcytic anemia (hemoglobin 6.2 g/dL), leukocytosis with neutrophilia (white blood cell count of $55.9 \times 10^9/L$, absolute neutrophil count of $52.1 \times 10^9/L$), and thrombocytopenia (platelet count of $90 \times 10^9/L$). The patient was admitted to the hematology ward with an impression of lymphoma and was referred to the ORL team for an excisional biopsy. Upon examination, there were multiple enlarged LN bilaterally in the neck (Figure 3A), axillae, and inguinal regions. The right torus tubarius was bulky compared with the left side; however, no obvious mass was identified in the nasopharynx or FOR on naso-endoscopy (Figure 3B). Other head neck examinations were unremarkable. Excision biopsy of the left level V cervical LN

was performed. HPE and IHC studies showed metastatic squamous cell carcinoma. CT scans of the brain, neck, thorax, abdomen, and pelvis were performed to identify the primary tumor. The CT scan showed mild thickening of the right torus tubarius compared with the left side, effacement of the right FOR, and no enhancing lesion (Figure 4A). Multiple enlarged LN were present in the cervical, axillary, mediastinal, abdominal, and inguinal regions (Figures 4B, 4C, 4D, 4E). In addition, there were multiple hypodense lesions in the liver and widespread lytic lesions in the pelvis, bilateral femora, spine, sternum, ribs, and bilateral humeri. A biopsy taken from the right FOR confirmed non-keratinizing NPC. Palliative chemotherapy was planned, but he developed sepsis secondary to pneumonia and died before initiation of chemotherapy.

Case 3

A 55-year-old woman, with no underlying medical illness, presented with painless left-sided neck swellings of 4 months' duration and bilateral axillary and inguinal swellings of 1 month's duration. It was



Figure 2. Multiple enlarged lymph node at left level II, III, and IV (A). No obvious mass in the nasopharynx (yellow star) or the Fossa of Rosenmüller (yellow arrow, left; yellow arrowhead, right) on naso-endoscopic examination (B).

LN: Lymph node

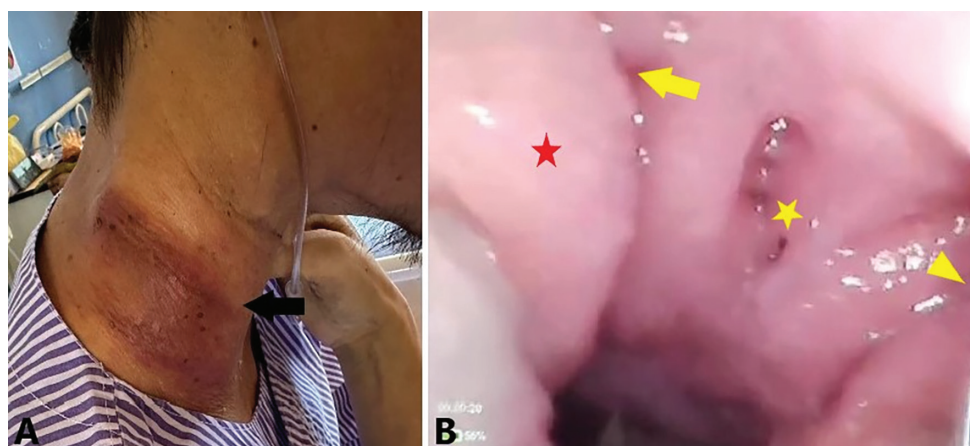


Figure 3. Huge right neck swelling with inflamed overlying skin (A). The right torus tubarius (red star) is bulky compared with the left side; however, no obvious mass is identified in the nasopharynx (yellow star) or the Fossa of Rosenmüller (yellow arrow, right; yellow arrowhead, left) on naso-endoscopic examination (B).

associated for 1 month with abdominal distension, shortness of breath, loss of appetite and weight loss, intermittent fever, and night sweats. There was no nasal or otological symptoms. The full blood picture revealed hypochromic microcytic anemia (hemoglobin 6.4 g/dL), leukocytosis with neutrophilia (white blood cell count $34.2 \times 10^9/L$, absolute neutrophil count $26 \times 10^9/L$), and thrombocytopenia (platelet count $87 \times 10^9/L$). The patient was admitted to the hematology ward with an impression of lymphoma, and CT scans of the neck, thorax, abdomen, and pelvis were performed. The CT scan demonstrated mild thickening of the left torus tubarius, compared with the right side, and effacement of the left FOR, with no enhancing lesion seen (Figure 5A). There were multiple enlarged LN in the cervical, axillary, mediastinal, abdominal, and pelvic regions (Figures 5B, 5C and 5D), as well as hepatosplenomegaly and a right lung nodule. The subsequent patient was referred to the ORL team for an excision biopsy. Upon examination, the patient was febrile, tachypneic, with multiple enlarged LNs in the neck bilaterally (Figure 6A), axillae, and inguinal regions. There was prominence of the left torus tubarius compared with the right side; however, no obvious mass was identified in the nasopharynx or the FOR regions on naso-endoscopy (Figure 6B). Other head neck examinations were unremarkable. The abdomen was distended, and hepatosplenomegaly was present. A tru-cut biopsy of the left cervical LN was performed. HPE and IHC studies showed metastatic squamous cell carcinoma. A biopsy from the left FOR confirmed non-keratinizing NPC. The patient was not fit for palliative chemotherapy; subsequently, her condition deteriorated, and the patient died during the same admission.

DISCUSSION

NPC is a rare malignant lesion in Western countries but is highly prevalent in Asia (1,3,4). East and Southeast Asia are classified as endemic areas for NPC, with 70% of new cases reported in 2018 originating from these areas, and NPC was listed as the eighth leading cause of cancer deaths in Southeast Asia (3,4). Middle-aged men with a positive family history and a history of Epstein–Barr virus (EBV) infection, smoking, and consumption of preserved food or salted fish are the group most frequently affected in endemic areas (1,4,5).

The most common presenting symptom is neck swelling, followed by nasal and ear symptoms (1,5,6). Level II cervical LN is the most common site followed by level III, V and IV, while level I, VI and supraclavicular regions are rarely involved (8). Based on the literature and to the best of our knowledge, generalized LN involvement is more suggestive of lymphoproliferative or hematological malignancies, such as lymphoma, and is extremely rarely associated with NPC. The association between generalized lymphadenopathy and the prognosis of NPC has not been described in the literature. In this case series, all patients had distant metastases and were thus stage IVB; we believed that generalized lymphadenopathy could be a poor prognostic indicator.

Pre-treatment hemoglobin, white blood cell, and platelet levels have been investigated in solid tumors, including NPC, and have shown prognostic significance (7,9). A study conducted in China with a total of 658 patients showed that 3.3%, 9.1%, and 2.7% of patients had anemia, leukocytosis, and thrombocytosis, respectively (9). Another study in Indonesia with a smaller sample size (48 patients) showed

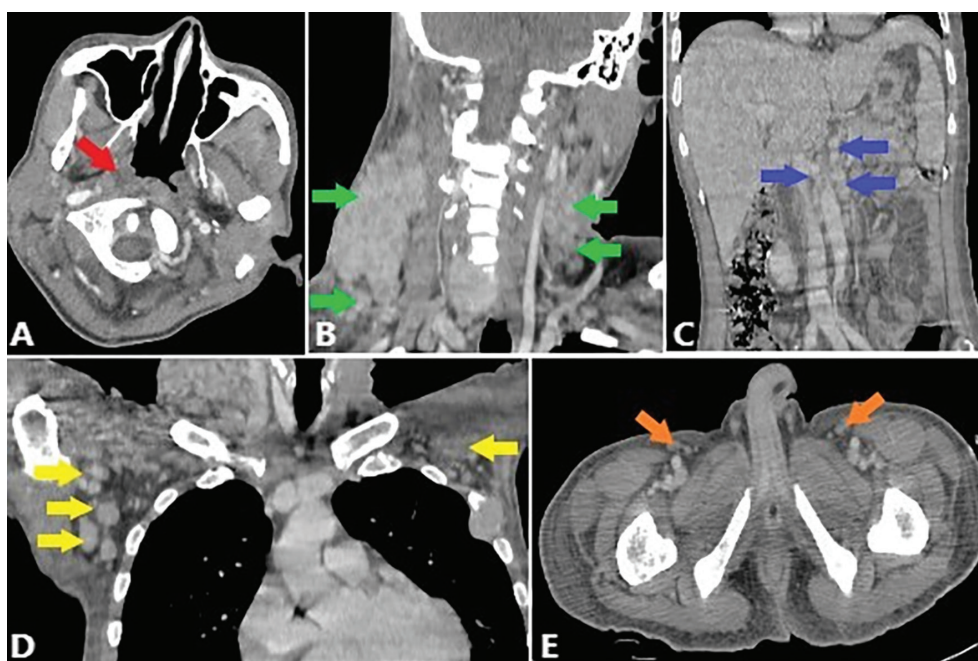


Figure 4. Contrast-enhanced CT scan of neck, thorax, abdomen, and pelvis. An axial image at the level of the nasopharynx shows mild thickening of the right torus tubarius compared with the left side and effacement of the right FOR (red arrow), with no enhancing lesion seen (A). A coronal image of the neck shows bilateral cervical nodes at levels II, III, IV, and V (green arrow; B). A coronal image of the abdominal region shows multiple enlarged para-aortic LNs (blue arrow; C). A coronal image of the thorax shows multiple enlarged axillary LNs (yellow arrow) (D). The axial image of the pelvis (E) depicts bilateral inguinal LN enlargement (orange arrowhead).

CT: Computed tomography, LN: Lymph node, FOR: Fossa of Rosenmüller

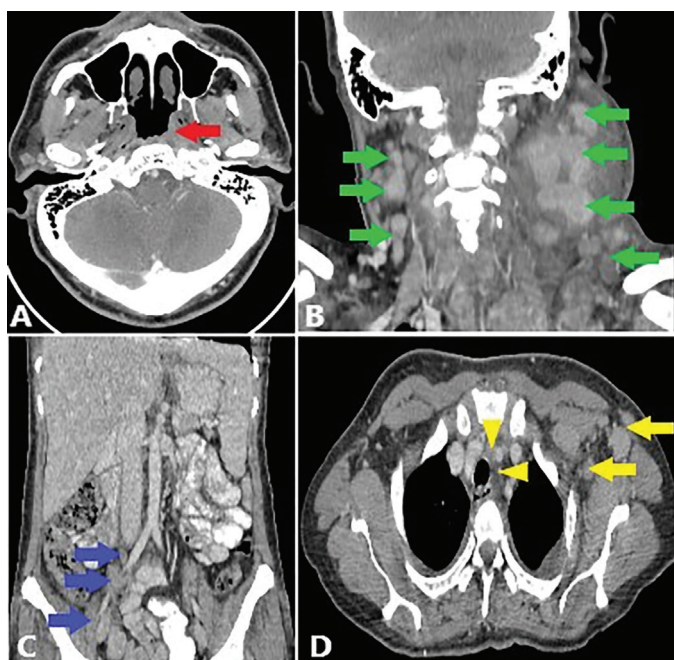


Figure 5. Contrast-enhanced CT scan of neck, thorax, abdomen and pelvis. Axial image at the level of the nasopharynx shows mild thickening of the left torus tubarius compared with the right side, with effacement of the left FOR (red arrow), without any enhancing lesion seen (A). Coronal image of the neck shows bilateral cervical nodes at levels II, III, IV and V (green arrow) (B). Coronal image of the abdomen and pelvis shows multiple enlarged LNs surrounding the right common and external iliac vessels (blue arrow; C). An axial image of the thorax shows multiple enlarged left axillary and paratracheal LNs (yellow arrow and yellow arrowhead, respectively) (D).

CT: Computed tomography, LN: Lymph node, FOR: Fossa of Rosenmüller

a higher percentage of patients with anemia, leukocytosis, and thrombocytosis: 52.1%, 29.2%, and 43.8%, respectively (7). These discrepancies could be due to many factors, such as the sample sizes of the studies, the stages of the disease at presentation, and the cutoff values used. Thrombocytopenia is rarely investigated and is less frequently associated with NPC compared with thrombocytosis. Chen et al. (10) reported that 10.1% and 15.8% of NPC patients had thrombocytopenia and thrombocytosis, respectively. Another study by Susilawati et al. (7) showed that 6.2% of NPC patients had thrombocytopenia, while 43.8% of patients had thrombocytosis. Anemia, leukocytosis, and thrombocytosis are well-established poor prognostic factors for NPC (7,9,11,12). Although a small number of studies investigated thrombocytopenia, they consistently showed an unfavorable prognosis in this patient category (7,10).

According to the United States National Cancer Institute (7), severe and extremely severe anemia are defined as hemoglobin levels of 6.5–7.9 g/dL and <6.5 g/dL, respectively. In this case series, one patient presented with severe anemia and two patients with extremely severe anemia. The causes of anemia in NPC patients are complex and multifactorial. It could be due to poor oral intake and nutrition in cancer patients, reduced hemoglobin production or hemolysis, and bleeding from the tumor. Tumor cells secrete the hormones serotonin and bombesin, which result in poor appetite, leading to poor nutrition (7). The tumor cells may also induce cytokine production, which can suppress erythropoiesis and the response of erythroid progenitor cells to erythropoietin and can cause hemolysis (9). An enlarging tumor is prone to bleeding due to the formation of neovessels that lack smooth muscle and contractile properties. Tumor hypoxia secondary to severe anemia may activate hypoxia-inducible factor-1, thereby promoting tumor metastasis (9). Leukocytosis is often associated with neutrophilia, as observed in the present cases, and both indicate a poor prognosis in NPC patients (11,13). Leukocytosis and neutrophilia are defined as leukocyte count more than $10 \times 10^9/L$ and $8 \times 10^9/L$ respectively in most of the studies (11). The underlying inflammation, immune response, and cytokine release within the tumor microenvironment stimulate leukocyte and neutrophil proliferation (9,13). This chronic inflammatory process in malignancy is of paramount importance

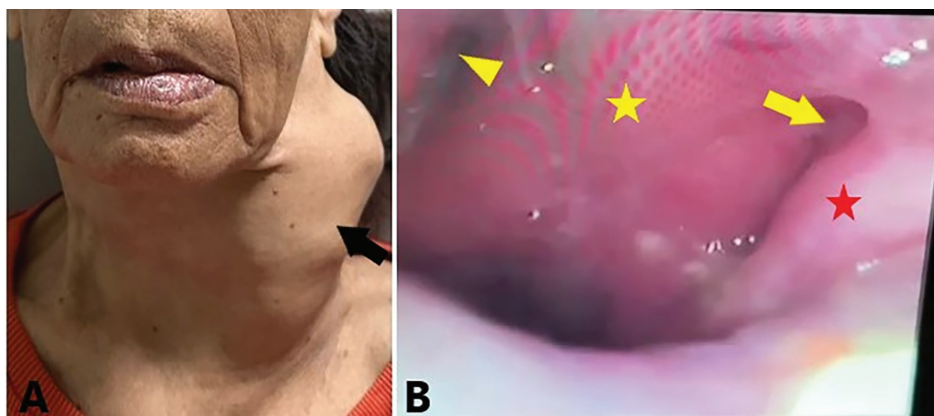


Figure 6. Huge left neck swelling with matted cervical LN (A). The left torus tubarius (red star) was prominent compared with the right side; however, no obvious mass was identified in the nasopharynx (yellow star) or Fossa of Rosenmüller (yellow arrow, left; yellow arrowhead, right) on nasoscopy examination (B).

LN: Lymph node

and has been found to promote tumor invasion, progression, and metastasis (13). Apart from this process, leukocytosis in solid tumors could be due to infection, use of corticosteroids, intoxication, severe hemorrhage, bone marrow metastases, paraneoplastic leukemoid syndrome, and use of granulocyte colony-stimulating factor (11,14).

Thrombocytosis in patients with NPC has been defined differently in the literature. Chen et al. (10) and Gao et al. (12) defined thrombocytosis as a platelet count greater than $300 \times 10^9/L$; Susilawati et al. (7) defined thrombocytosis as a platelet count greater than $380 \times 10^9/L$ (7), while Qiu et al. (9) defined thrombocytosis as a platelet count greater than $400 \times 10^9/L$. In contrast, the definition of thrombocytopenia is more consistently defined as a platelet count less than $150 \times 10^9/L$ (10,12). The cause of platelet proliferation in malignancy is still unclear, but it is believed to be secondary to the production of cytokines, such as interleukin 6 and thrombopoietin (10,12). Platelets secrete proangiogenic cytokines, vascular endothelial growth factor and thymidine phosphorylase, which are important in tumor invasion and progression (10). Thrombocytopenia may develop in patients with NPC secondary to diffuse infiltration of tumor cells into the bone marrow or spleen, immune-mediated mechanisms, EBV infection, or paraneoplastic syndrome (7,10,15). Thrombocytopenia secondary to bone marrow infiltration and bony metastases, as observed in the cases at presentation, categorized patients as having advanced disease (stage IVB) and significantly reduced the survival rate. A study conducted by Chen et al. (10) showed that thrombocytopenia, compared with a moderate platelet count, was an unfavorable prognostic factor for overall survival in patients receiving concurrent chemoradiotherapy and had a greater negative effect than the thrombocytosis group.

In addition to prognostic significance, combinations of generalized lymphadenopathy, severe anemia, leukocytosis, and thrombocytopenia in the cases had misdirected us toward the diagnosis of lymphoma at the initial presentation. This atypical presentation of NPC significantly delays diagnosis and treatment and is generally associated with an unfavorable prognosis. Another challenge in the diagnosis of the presenting cases was the submucosal location of the tumor and the absence of an obvious mass in the nasopharynx or the FOR on naso-endoscopy and CT scan. A prominent unilateral torus tubarius, as seen in our cases 2 and 3, may suggest the presence of a submucosal tumor, and a deep biopsy should be performed in suspected cases. The nasal biopsy was not performed at the initial presentation in our cases because the patients' general clinical presentations were more suggestive of lymphoma. MRI is an excellent investigation for submucosal NPC because it can delineate soft tissue better than a CT scan (3), but it is not available at our center. Another imaging modality that helps localize the primary tumor is the combination of positron emission tomography and CT scan, which shows high uptake of the radioactive tracer (fluorodeoxyglucose) by the highly metabolic malignant cells. This imaging is currently considered the gold standard for cancer of unknown origin and should be performed prior to biopsy; however, it is not available in many centers, including ours.

Fine Needle Aspiration Cytology (FNAC) should be the first investigation of choice in patients with suspected head and neck malignancy to avoid the risk of tumor seeding to the skin and upstaging the cancer. However, in cases with suspected lymphoma,

excisional or tru-cut biopsies are preferred because FNAC cannot provide sufficient tissue for diagnosis and subtype determination. In this case series, we performed excisional biopsies in two patients and a through-cut biopsy in one patient. All HPE results showed metastatic squamous cell carcinoma, whereas the IHC study had a limited role in determining the primary site. Special stains for NPC, such as EBV-encoded non-polyadenylated RNAs, EBV nuclear antigen 1, and latent membrane protein 1 and 2, are considered helpful (16), but they were not available at our center.

All patients in these cases were at stage IVB and were indicated for palliative chemotherapy. All of them had poor ECOG performance status at diagnosis and died within 4 months of diagnosis. Clinicians should be aware of these atypical presentations, and a prompt diagnosis should be made to avoid delays in treatment.

CONCLUSION

NPC is a rare cancer globally but is highly prevalent and endemic in East and Southeast Asia. The patients may present with atypical features that can mimic other malignant lesions. Generalized lymphadenopathy, severe anemia, leukocytosis, and thrombocytopenia are typical presentations of lymphoma but are atypical of NPC. These presentations not only cause diagnostic confusion but also are associated with significant poor prognostic indicators. Awareness of these atypical presentations is of paramount importance to avoid delays in management and worsening of overall survival.

Ethics

Informed Consent: Informed consent was obtained from all patients for publication.

Footnotes

Conflict of Interest: No conflict of interest was declared by the author.

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