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CASE REPORT

Leukemoid Reaction and Sudden Hearing Loss in Early Cervical Cancer: A Case Report and Review of the Literature

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Background: The manifestation of a leukemoid reaction in the cervical cancer is an uncommon occurrence. Three cases of advanced, recurrent or metastatic cervical cancer with leukoid reaction have been reported in the past, but no early cervical cancer with leukoid reaction has been reported. Paraneoplastic neurological syndromes (PNS) are rare and have not been reported in cervical cancer.

Case Presentation: A 38-year-old woman presented was admitted to hospital because of sudden hearing loss in her right ear, and routine blood tests showed abnormally elevated white blood cells and neutrophils (WBC: 43.87*109/L, NEU: 39.63×10^9/L). Cervical biopsy and pathological examination revealed cervical squamous cell carcinoma. Infection and hematological diseases such as leukemia and bone marrow metastasis were ruled out. After operation WBC and NEU counts decreased and remained at normal levels and the hearing condition of her right ear was significantly improved than before. No leukopenic drugs or neurotrophic agents that improve hearing were used during the treatment period.

Conclusion: This is the first case of cervical cancer presenting with sudden deafness and the first case report of early cervical cancer complicated by a leukemoid reaction, which may be related to a paraneoplastic neurological syndrome.

Keywords: leukemoid reaction, paraneoplastic neurologic syndrome, cervical cancer

Introduction

Cervical cancer ranks as the second most prevalent form of cancer among women globally, usually characterized by symptoms such as contact vaginal bleeding. Early cervical cancer can achieve a good prognosis through surgery or radiotherapy and chemotherapy, while some patients with advanced and recurrent cervical cancer can also achieve long-term survival under immunotherapy and targeted drug therapy. Cervical cancer with leukoid reaction is rarely reported. Three cases of advanced, recurrent or metastatic cervical cancer with leukoid reaction have been reported in the past, but no early cervical cancer with leukoid reaction has been reported. There was no case of cervical cancer with sudden deafness as the first symptom. We report on a patient diagnosed with early-stage (International Federation of Gynecology and Obstetrics, FIGO IB2) cervical squamous cell carcinoma with sudden hearing loss and leukoid reaction. Leukostasis was a complication of hyperleukocytosis, including chronic myeloid leukemia. A large number of white blood cells can block the microcirculation of blood vessels and capillary lymphatic vessels, resulting in a series of clinical symptoms. Nevertheless, otological manifestations are exceedingly uncommon. Paraneoplastic neurological syndromes (PNS) were originally delineated as neurological syndromes of indeterminate etiology frequently associated with malignancies, and these conditions often present themselves prior to the identification of the underlying neoplastic disease. However, PNS has a low incidence and is difficult to diagnose effectively. This is the first case of cervical cancer with recurrent hearing loss as the first symptom. The clinical and histological characteristics are detailed. The literature pertaining to these exceptional cases has been subjected to a thorough review.

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Case Presentation

Case Report

A 38-year-old woman presented was admitted to Dong'e County People's Hospital because of sudden hearing loss in her right ear on February 4, 2024. The hearing examination revealed a decrease in the mid-low frequencies in the right ear, and the patient felt that she was close to deafness in the right ear. Hearing in left ear was normal. During hospitalization, a gynecological examination revealed a cauliflower-like mass with a diameter of 4 cm on the cervix without contact vaginal bleeding. Cervical biopsy and pathological examination revealed cervical squamous cell carcinoma. Routine blood tests showed abnormally elevated white blood cells and neutrophils (WBC: 43.87*10^9/L, NEU: 39.63×10^^{9}/L).

The patient was referred to Shandong Tumor Hospital Affiliated to Shandong First Medical University on February 17, 2024. Gynecological examination: a cauliflower-like mass on the cervix, about 4cm in diameter, the vaginal vault and vaginal wall are smooth, without tumor invasion, the paracervical tissue was soft and no tumoral thickening was palpable. The patient underwent routine blood test again, and the results showed that leukemia and neutrophils continued to increase (WBC: 45.04*109/L, NEU: 40.62×10^9/L). However, the patient has never had obvious symptoms of infection such as fever and cough, and C-reactive protein (CRP) and procalcitonin (PCT) had always been at normal levels. No obvious abnormalities were found in hematological tumor markers, including squamous cell carcinoma antigen (SCC), carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125) and carbohydrate antigen 199 (CA199). Positron Emission Tomography-Computed Tomography (PET-CT) examination showed cervical cancer accompanied by standardized uptake value (SUV) hypermetabolism, diffuse hypermetabolism in multiple bones involved; splenomegaly accompanied by hypermetabolism; hematological diseases not excluded, bone marrow puncture/biopsy recommended; No obvious space occupying lesions, hemorrhage and infarction of cranium; No obvious metastasis or tumor signs were found in other regions of the body (Figure 1). At the same time the patient underwent bone marrow puncture to rule out hematological diseases such as leukemia and bone marrow metastasis. The cytological examination of the bone marrow aspiration revealed no presence of abnormal cells, and the proportion of granulocytes (89.1%) increased. BCR: ABL1, p190 fusion gene results were negative. After ruling out infection and blood system diseases, the patient was diagnosed with cervical cancer (IB2 FIGO2018), combined with leukemia-like reaction and sudden hearing loss of right ear.

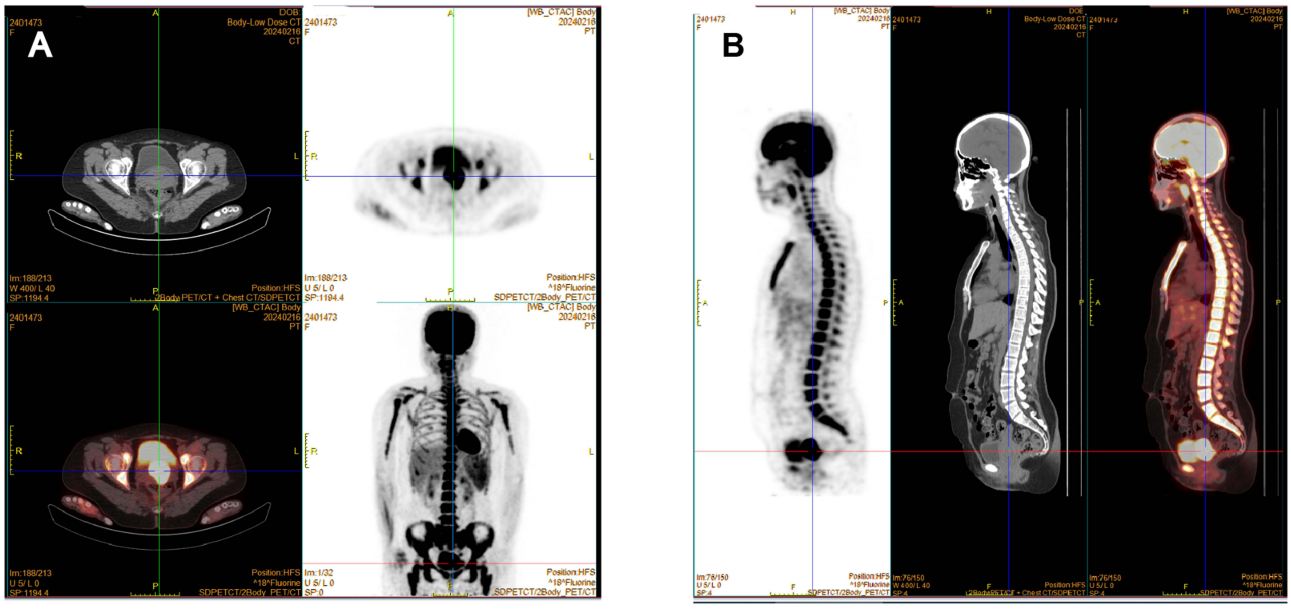


Figure 1 (**A**) PET-CT examination cross-sectional image showed cervical cancer accompanied by SUV hypermetabolism, diffuse hypermetabolism in multiple bones involved; splenomegaly accompanied by hypermetabolism; hematological diseases not excluded, bone marrow puncture/biopsy recommended; (**B**) Sagittal images showed no obvious metastasis or tumor signs were found in other parts of the body. The center of the cross is cervical tumor.

Extensive hysterectomy + bilateral salpingo-oophorectomy + pelvic lymph node dissection + para-aortic lymph node dissection was carried out under general anesthesia on February 28, 2024. A repeat blood routine test the day before surgery showed that the white blood cell (WBC) count was 51.47×10^^{9}/L. Routine pathological examination showed: squamous cell carcinoma, G3, Vertical infiltration range: deep 1/3, 4.5cm in diameter, lymphovascular invasion (LVSI)+, no lymph node metastasis (para-aortic lymph nodes 0/7, pelvic lymph nodes 0/28) (Figure 2). The postoperative diagnosis was revised to cervical squamous cell carcinoma stage IB3 (FIGO2018). White blood cells dropped significantly on the first day after surgery, the white blood cell count was 33.78×10^9/L and the neutrophil count was 31.01×10^^{9}/L. On postoperative day 11, the patient's WBC and NEU counts decreased and remained at normal levels (2024-03-10 WBC 5.78×10^9/L, NEU 4.21×10^9/L) (Figure 3). No white blood-lowering drugs were used during this period, and antimicrobial drugs were discontinued 48 h after surgery. Eleven days after the operation, the patient felt that the hearing condition of her right ear was significantly improved than before. A retest of the hearing test showed that the hearing in the mid-frequency area of the right ear was better than before, but the low-frequency area was still weak. The patient was transferred to the oncology department to receive adjuvant radiotherapy and chemotherapy.

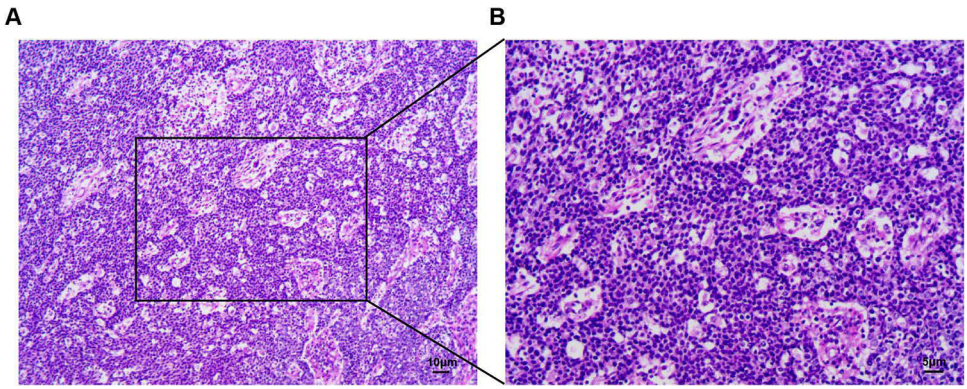
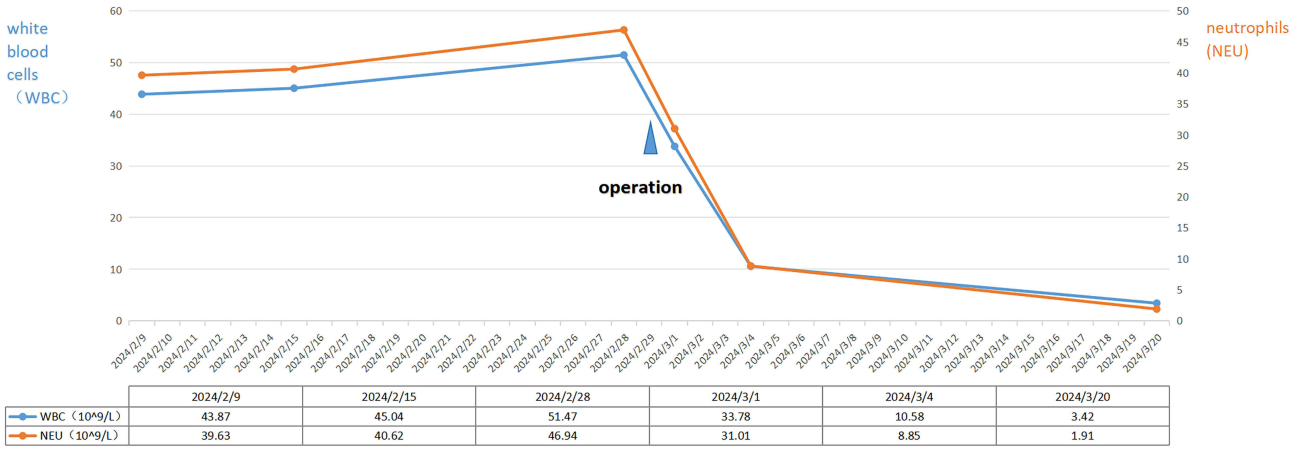


Figure 2 Postoperative routine pathological examination of cervical cancer (**A**) 10X Microscopic examination reveals enlarged tumor cell nuclei with hyperchromasia, high nuclear-to-cytoplasmic ratio, poor squamous differentiation, and frequent mitotic figures. (**B**) 20X Microscopic examination display more specific pathological characteristics of tumor cells.



	2024/2/9	2024/2/15	2024/2/28	2024/3/1	2024/3/4	2024/3/20
WBC（10^9/L）	43.87	45.04	51.47	33.78	10.58	3.42
NEU（10^9/L）	39.63	40.62	46.94	31.01	8.85	1.91

Figure 3 Trend chart of changes in WBC and NEU counts (The blue triangle represents surgery).

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Discussion

The incidence of cervical cancer leukemia is low, bone marrow metastasis, hematological diseases and severe infection should be excluded. Leukemia-like reaction is usually associated with abnormal increases in granulocyte colony-stimulating factor (G-CSF), interleukin-6 (IL-6) and granulocyte-macrophage colony-stimulating factor (GM-CSF). This case of cervical carcinoma complicated with sudden deafness was considered to be related to paraneoplastic nerve syndrome or leukostasis. It is difficult to accurately diagnose early cervical cancer with paraneoplastic syndrome, especially the rare paraneoplastic syndrome. Early diagnosis and timely anti-tumor therapy can obtain a good prognosis.

Data Analysis

When the patient was diagnosed with hearing loss, an abnormal increase in white blood cells was found, and the white blood cell count reached the highest point before surgery. During this period, the patient never developed symptoms of infection such as fever or cough. At the same time, no signs of severe infection were found in blood tests such as PCT, CRP and PET-CT examinations. Respiratory tract, urinary tract, hematogenous and other infections have been ruled out. There was no obvious necrosis and purulent secretions in local cervical tumors, and the tumor was solid. PET-CT showed diffuse hypermetabolism in multiple bones. But bone marrow aspirates and biopsy distinguished LR from chronic myelogenous leukemia (CML) and bone marrow infiltration of cervical cancer. In our case, the patient's WBC and NEU counts gradually decreased to normal levels after undergoing radical surgery for cervical cancer. With the white blood cell gradually returning to normal, the hearing of the right ear of the patient gradually recovered. At the same time, there were no obvious intracranial space occupying lesions and vascular diseases such as cerebral infarction and cerebral hemorrhage in craniocerebral CT examination. We consider that this patient has cervical cancer probably with two kinds of paraneoplastic syndrome, including leukemia-like reaction and nervous system paraneoplastic syndrome.

Leukemoid Reaction in Cervical Cancer

Leukemia-like reactions have been noted in many kinds of solid tumors, which was related to poor prognosis.[1,2] The incidence of this issue among individuals with nonhematologic cancer is not well-defined, with estimates ranging from 1% to 4% based on small case series.[3,4] Cervical cancer with leukemia-like reaction was rarely reported. A total of three previous cases of cervical cancer with leukemia-like reaction were reported, including one case of advanced cervical cancer[5] and two cases of recurrent cervical cancer.[6,7] This is the first case of early cervical cancer complicated with leukemia-like reaction, and the first case of cervical cancer with paraneoplastic syndrome of the nervous system. Patients with cervical cancer complicated with leukemia-like reaction tended to exhibit a prognosis of poor quality, a significant tumor burden, and a compromised condition. According to the literature, the survival time of stage IVb cervical cancer complicated with LR was only 6 weeks. Two cases of early cervical cancer complicated with LR after operation, the time of recurrence was 15 days and 68 days after operation, respectively. Previous studies showed that the degree of leukemoid reaction was found to be associated with the timing of mortality. If the WBC reaches 100×109 /L, the patients could not tolerate anti-tumor therapy such as radiotherapy and chemotherapy because of their unstable clinical condition.[8] For recurrent cervical cancer combined with LR that could tolerate chemotherapy, the prognosis was relatively better. Due to early diagnosis and timely operation, the symptoms of white blood cells and nervous system returned to normal after radical operation, and the prognosis was good.

Mechanism of Leukocyte-Like Reaction

Paraneoplastic syndrome is usually caused by abnormal cytokines produced by tumors, which lead to different clinical manifestations of patients. Leukemia-like reaction as a common paraneoplastic syndrome is usually associated with abnormal increases in cytokines such as IL-6, GM-CSF and G-CSF. A multitude of nonhematopoietic malignant neoplasms have been shown to produce G-CSF, with many exhibiting a prognosis that is unfavorable.[9] Abnormally elevated G-CSF and IL-6 could be detected in the serum of leukemia-like patients. The staining of IL-6 and G-CSF was predominantly detected in the cytoplasmic compartment of cancer cells. Previous studies have showed that when G-CSF was overexpressed by cancer cells, it can promote the proliferation of myeloid-derived suppressor cells (MDSC). After

MDSC enters the lymph nodes, it can prevent T lymphocytes activated by dendritic cells from clearing tumor cells. This was thought to be related to the rapid growth of tumors and poor clinical prognosis.

Paraneoplastic Neurological Syndromes (PNS) and Sudden Hearing Loss

PNS were originally delineated as neurological syndromes of indeterminate etiology frequently associated with malignancies, and these conditions often present themselves prior to the identification of the underlying neoplastic disease.[10] Epidemiological study showed that prevalence of PNS was determined to be 4.37 per 100,000 of the population, while the incidence rate stood at 0.89 per 100,000 person-year.[11] Paraneoplastic neurological syndromes are generally divided into two types: High-risk phenotypes (include encephalomyelitis, limbic encephalitis, rapidly progressive cerebellar syndrome, sensory neuronopathy, gastrointestinal pseudo-obstruction, and Lambert–Eaton myasthenic syndrome) and intermediate-risk phenotypes (include encephalitis (other than limbic encephalitis), brainstem encephalitis, Morvan's syndrome, isolated myelopathy, stiff person syndrome, and polyradiculoneuropathies). The detection of antibodies targeting neural antigens expressed by tumors, known as onconeural antibodies, has proven to be of paramount importance in the diagnosis of paraneoplastic syndromes. Nevertheless, PNS may manifest in the absence of onconeural antibodies, indicating that the presence of such antibodies is not the sole criterion for the identification of a neurological syndrome as paraneoplastic. An additional newly identified autoantibody linked to a brainstem-predominant presentation and the presence of gonadal and extra-gonadal germ cell tumors is KLHL11 IgGA. A considerable proportion of these patients also manifest symptoms of paraneoplastic cochleovestibulopathy, which is characterized by auditory impairment and/or vertiginous sensations. Additionally, brainstem involvement has been documented in association with other classical onconeural antibodies.[12–14]It is acknowledged that sensory neural hearing impairment and tinnitus manifest as initial symptoms of the neurological syndrome associated with KLHL11-IgG. Due to the limitation of detection conditions, the patient did not detect antibodies related to paraneoplastic syndrome of the nervous system. However, with the reduction of tumor load after operation, the hearing of the patients gradually recovered. It was considered that the hearing loss might be the paraneoplastic nerve syndrome caused by cervical cancer.

Sudden Hearing Loss and Leukostasis

Leukostasis was a complication of hyperleukocytosis, including chronic myeloid leukemia, which could lead to a variety of serious clinical complications, such as renal failure, respiratory failure or intracranial hemorrhage. Extramedullary manifestations of Chronic myelomonocytic leukemia (CMML) can affect multiple organs such as the spleen, lymph nodes and liver. Nevertheless, otological manifestations are exceedingly uncommon and have predominantly been documented in cases of chronic myeloid leukemia.[15] Some patients with chronic myeloid leukemia showed hearing loss, which was related to microcirculatory disturbance caused by leukocyte stasis, and usually showed bilateral hearing loss or loss.[16] Resende documented a case of abrupt bilateral hearing loss in an individual diagnosed with Chronic Myeloid Leukemia (CML). They posited that the hearing impairment was precipitated by the condition of hyperleukocytosis, leading to leukostasis and subsequent hyperviscosity within the labyrinthine artery and additional diminutive arteries of the vertebrobasilar system.[17] The comprehensive analysis of the data indicates the occurrence of hyperleukocytosis, accompanied by leukostasis and hyperviscosity syndrome. There was no clear reports of hearing loss caused by leukemia-like reaction, but hyperleukocytosis and hyperviscosity syndrome caused by leukemia-like reaction may also lead to hearing loss by blocking the circulation of arterioles.

Conclusion

As far as our understanding extends, this constitutes the inaugural case report of an early-stage cervical cancer patient presenting with a leukemoid reaction who has attained a favorable prognosis as a result of early detection, prompt surgical intervention, and timely administration of chemoradiotherapy. The previously reported cases of cervical cancer complicated with leukemia-like reaction were all advanced or recurrent patients with poor prognosis. This is the first case of cervical cancer with sudden deafness, which may be related to paraneoplastic neurologic syndrome or leukostasis caused by hyperleukaemia.

Declaration of Patient Consent

Formal written consent for the publication of this case report and any associated images was procured from the patient. The patient duly executed an informed consent document.

Ethics Approval and Consent to Participate

Written informed consent was obtained from the patient for publication of the health information in anonymised form. Institutional review board approval was not required, given the patient provided written consent.

Disclosure

The authors report no conflicts of interest in this work.

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