Warm autoimmune hemolytic anemia following definitive chemoradiotherapy for cervical cancer: A case report

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Received December 10, 2025; Accepted May 26, 2026

DOI: 10.3892/ol.2026.15682

Abstract. Although autoimmune hemolytic anemia (AIHA) is a well-known paraneoplastic syndrome in hematologic malignancies, it has rarely been reported in solid tumors. Documented cases of secondary warm AIHA (wAIHA) linked to solid tumors, particularly cervical cancer, are exceedingly rare. The present study reports 1 case of wAIHA occurring in a 73-year-old patient following radical chemoradiotherapy for cervical cancer. To the best of our knowledge, this association between wAIHA and cervical cancer has not been previously reported. The present case report highlights cervical cancer as a novel etiology of secondary AIHA and emphasizes the need for clinical vigilance to avoid diagnostic delays in post-treatment anemia.

Introduction

Autoimmune hemolytic anemia (AIHA) is a rare disease caused by immune dysfunction leading to hyperactive B cells producing autoantibodies against red blood cells. These antibodies bind to red blood cells and may activate complement systems, resulting in hemolysis. International data indicates an annual incidence rate of 0.8-3.0/100,000 cases worldwide (1). Based on the type and thermal characteristics of the autoantibody, AIHA can be classified into three types: Classic warm AIHA (wAIHA), cold agglutinin disease (CAD) and mixed AIHA. Notably, ~50% of wAIHA cases are secondary and associated with a number of underlying medical disorders including blood malignancies, solid tumors, autoimmune diseases, infections, solid organ and hematopoietic stem cell transplants, and numerous drugs (including antibiotics, immune checkpoint inhibitors anti-programmed cell death protein 1, programmed death-ligand 1 and cytotoxic T-lymphocyte associated protein 4) (2).

However, there are few reported cases of AIHA associated with solid tumors. Most cases involving solid tumors in AIHA have been documented in renal tumors, Kaposi's sarcoma, prostate tumors, ovarian tumors and non-small cell lung cancer (3-7). Analysis of previously reported cases of AIHA associated with solid tumors suggests that AIHA may occur before the diagnosis of malignant tumors, emerge concurrently with solid malignancies, or even manifest as a sign of cancer recurrence or complete remission following treatment (7). Cervical cancer has rarely been identified as a cause of AIHA. Although anemia is one of the most common post-treatment complications in cervical cancer patients (8), autoimmune hemolysis-induced anemia remains unreported. This rare etiology is often overlooked by clinicians, causing delays in treatment and potentially compromising treatment outcomes. The present study reports a case of wAIHA in a 73-year-old patient with cervical cancer after radical chemoradiotherapy, which, to the best of our knowledge, revealed this rare association for the first time.

Case report

A 73-year-old woman with >20 years natural menopause developed vaginal bleeding in November 2024. At first the patient did not take it seriously. In January 2025, the patient was initially admitted to Nanjing Gaochun People's Hospital (Nanjing, China). A colposcopy performed in January 2025 and revealed cervical squamous cell carcinoma (Fig. 1A), with human papilloma virus (HPV) 16 (a high-risk HPV type) detected using HPV testing. Pelvic MRI demonstrated a space-occupying lesion on the anterior cervical wall (Fig. 1B). The clinical stage was IB using the International Federation of Gynecology and Obstetrics 2018 staging system (9). Their hemoglobin (Hb) level was 14.4 g/dl prior to treatment. The patient refused surgical treatment and underwent pelvic radical radiotherapy (95% planning target volume; 45 Gy/25F) from February to March 2025, combined with cisplatin chemotherapy (55 mg/weekly for 5 weeks). The final cisplatin session was administered in March 2025. Serial blood counts during external beam radiotherapy did not show signs of myelosuppression in Hb, which was consistently >12 g/l. However, the

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Key words: autoimmune hemolytic anemia, cervical cancer, paraneoplastic syndrome, chemoradiotherapy, case report

patient experienced leukopenia and thrombocytopenia which improved following administration of human granulocyte colony-stimulating factor and thrombopoietin.

In March 2025, the patient began intracavitary brachytherapy with a prescribed total dose (DT) of 35 Gy/7F. By April 2025, when the DT reached 25 Gy/5F, a follow-up blood test showed Hb levels at 4.9 g/dl. The patient received supportive treatments including hematopoietic agents, erythropoietin and blood transfusions. Following this, in April 2025, brachytherapy continued. After finishing intracavitary brachytherapy, the Hb levels remained persistently low, although aggressive blood transfusion, erythropoietin and supportive treatment were adopted.

In May 2025, Hb was only 4.3 g/dl. Abnormal elevation of bilirubin levels, predominantly unconjugated bilirubin, were observed with total bilirubin 51.4 μmol/l and direct bilirubin 9.8 μmol/l. Laboratory examination showed the following: Irregular antibody screening, negative; direct antiglobulin test (DAT), positive; and indirect antiglobulin test (IAT), positive. The reticulocyte percentage was 21.07%. DAT was performed using monospecific anti-human globulin reagents against IgG and C3d. The result showed elevated monospecific anti-IgG levels (mono-Coombs IgG positive), confirming the diagnosis of autoimmune hemolytic anemia (AIHA). DAT and IAT were performed in the Department of Clinical Laboratory of Nanjing Gaochun People's Hospital (Nanjing, China) following routine clinical protocols. For DAT, the following reagents were used: anti-C3d (cat. no. 20153401143), anti-IgG (cat. no. 20153401142) and anti-human globulin (AHG; cat. no. 20153401144), all from Shanghai Blood Biological Medicine Co., Ltd. For IAT, LISS solution (batch no. 20231101; Changchun Bioxun Biotech Co., Ltd.) was used as enhancement medium, with IgG anti-D (cat. no. 20223401104; Shanghai Blood Biological Medicine Co., Ltd.) as positive control and IgG anti-Fya (cat. no. MFyaM21o-1; CE-Immun diagnostika GmbH) as specificity control; the same AHG reagent was employed. All tests followed the hospital's standard operating procedures.

Bone marrow smear cytology (Fig. 1C) was performed using standard Wright-Giemsa staining (methanol fixation at room temperature for 15 min, staining for 20 min). For H&E staining, specimens were routinely fixed in 3.7% neutral formalin at room temperature for 6-24 h, followed by conventional procedures including dehydration and paraffin embedding. The specimens were then cut into 3-μm-thick sections and stained with H&E for light microscopy examination. Hematoxylin staining was performed for 5 min and eosin staining for 3 min at room temperature. The slides were examined under a BX53 Olympus standard light microscope. The cytology (Fig. 1C) showed active proliferation of nucleated cells with a granulocyte-to-lymphocyte ratio of 2.12:1. Erythroid hyperplasia was prominent, with a marked increase in late-stage erythrocytes. Screening for underlying conditions (lymphoproliferative disorders, autoimmune diseases, infections, immunodeficiencies and medications) was performed by reviewing the patient's medical history, aforementioned laboratory blood tests and medication history. All results were negative or unremarkable except for the elevated direct Coombs test and hemolytic parameters. Therefore, secondary autoimmune hemolysis caused by cervical cancer was confirmed. After diagnosis, the patient initiated daily oral prednisone treatment at 50 mg. After 10 days medication, Hb levels rose to 11.9 g/dl. Subsequent weekly monitoring revealed Hb levels at 12.3 and 11.8 g/dl. The patient was followed up at the outpatient clinic every 2-4 weeks. Prednisone was gradually tapered over 8 weeks and completely withdrawn by the end of July 2025. At the most recent follow-up in April 2026, the patient remained asymptomatic with no evidence of hemolysis. Hemoglobin level was 12.5 g/dl. No recurrence of vaginal bleeding or other adverse events were observed.

Discussion

Anemia is common in patients with cancer. AIHA, as a rare manifestation of tumor-associated anemia, primarily occurs secondary to lymphoproliferative disorders including non-Hodgkin's lymphoma and an estimated 10% of chronic lymphocytic leukemia cases (10). The association between AIHA and solid malignant tumors has been rarely reported, including in gastric, ovarian, breast and kidney cancers (7,11). To the best of our knowledge, the present case reported the rare association between AIHA and cervical cancer for the first time. It is a further addition to tumor-associated AIHA and has notable clinical relevance.

Before confirming AIHA as secondary to cervical cancer, other more common related diseases must be ruled out. Firstly, the patient showed no hematopoietic or lymphatic system proliferative disorders. Secondly, all autoantibody tests of the patient were negative, and there was no recent history of infection, thus the association of AIHA with autoimmune diseases or infections were excluded. Previous studies (12,13) have indicated that cisplatin can cause non-immunologic protein adsorption onto the red blood cell (RBC) membrane; adsorbed proteins (including albumin, complement components and immunoglobulins, in particular IgG) can react with receptors on macrophages which can induce hemolytic anemia and lead to DAT positivity (14). This makes cisplatin a suspected cause of AIHA in the present patient. However in non-immunologic protein adsorption, the IAT is usually negative because the adsorbed proteins are not specific autoantibodies. The patient in the present study had a positive IAT, indicating the presence of circulating autoantibodies against native RBCs which is a hallmark of wAIHA. Furthermore, cisplatin-induced hemolysis usually develops during or shortly after drug administration and resolves spontaneously after drug withdrawal (15,16). The patient developed anemia >1 month after the last cisplatin chemotherapy, and the anemia still not alleviated after cisplatin withdrawal; therefore, cisplatin-induced immune hemolytic anemia was excluded.

The potential mechanism of AIHA secondary to solid neoplasms is not known. It is hypothesized that antibodies against tumor cells may crossly react with erythrocyte antigens, leading to hemolysis (7). Kitao *et al* (17) described an AIHA case secondary to colorectal cancer with ectopic band 3 expression, an anion transporter normally restricted to erythrocytes and renal cells. After further research, the authors found that ectopic band 3 expression was associated with

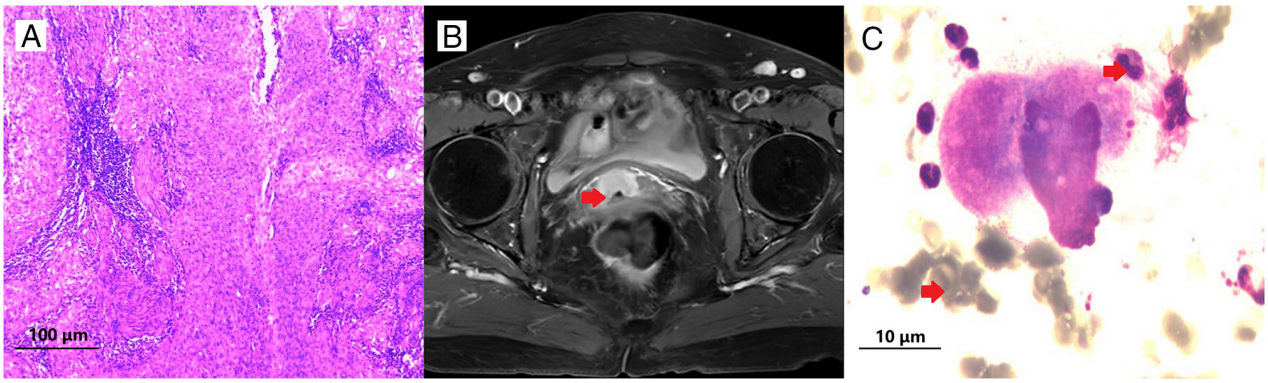

Figure 1. (A) H&E staining of cervical biopsy tissue showing characteristic squamous cell carcinoma (magnification, x100; scale bar, 100 μm). (B) A soft tissue mass measuring ~11x20x20 mm is observed on the anterior cervical wall, with relatively well-defined margins. Early dynamic enhancement showed notable contrast enhancement. The red arrow indicates the location of the tumor. (C) Bone marrow smear cytology showed active proliferation of nucleated cells with prominent erythroid hyperplasia, notably with a marked increase in late-stage erythrocytes (magnification, x1,000; scale bar, 10 μm). The red arrows indicate areas of active proliferation and late-stage erythrocytes.

increased erythrocyte membrane-bound IgG in patients with colorectal cancer which can lead to shortened RBC lifespan. Immunoprecipitation revealed increased anti-band 3 autoantibodies in serum from patients. Ectopic band 3 expression was also reported as a cause of mature ovarian teratoma-associated secondary autoimmune hemolytic anemia (18). This may be a potential mechanism of tumor-associated immune hemolysis. Future studies should investigate whether ectopic band 3 or cross-reactive antibodies serve a role in cervical cancer-associated AIHA.

The first-line treatment for wAIHA is usually glucocorticoids. However, during tapering and discontinuation, approximately a third of patients relapse and require further treatment (10). The anti-CD20 monoclonal antibody rituximab has become the first choice of second-line treatment, being able to induce hematologic responses in 70-80% of patients (1). For severely anemic patients whose Hb <8 g/dl, rituximab was recommended for first-line treatment in addition to steroids. Splenectomy is also an effective treatment option; the response rates can be 70-80%. Due to the increased risk of infection and thrombosis, splenectomy is rarely used today and is only recommend as a the third-line or subsequent treatment (19). Treatment for suspected complement-mediated hemolysis can include complement pathway inhibitors such as eculizumab (anti-C5) and sutimlimab (anti-C1s) (20). For patients resistant to or relapsing after rituximab and not suitable for splenectomy, the use of cytotoxic immunosuppressants such as azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, bortezomib might be considered, relying predominantly on evidence from small retrospective series and case reports (21,22).

The treatment of malignant tumor-associated AIHA has not been well established. The efficacy of steroids varies considerably among different populations. Puthenparambil *et al* (7) found that patients who had a response to resection of the tumor were often resistant to steroid treatment before surgery, while some hematologic responses to steroids were observed in patients with metastatic cancer. However, some cases of patients with AIHA secondary to metastatic cancer who received steroid therapy showed no efficacy, and the disease was controlled by palliative chemotherapy (23). In the present case, the patient had undergone radical concurrent chemoradiotherapy. Under these circumstances, the use of glucocorticoids led to notable improvement in anemia. In the present case, glucocorticoids were effective, supporting their consideration as a first-line option in similar patients, although responses may vary as noted in the literature. For patients unresponsive to glucocorticoids, some may benefit from tumor resection (even in metastatic cases), while some might respond to antitumor therapy.

The present case showed that autoimmune hemolysis is a potential cause of anemia after chemoradiotherapy in patients with cervical cancer, and it is occasionally difficult to distinguish from drug-induced hemolytic anemia and myelosuppression. Therefore, when unexplained anemia occurs after chemoradiotherapy in patients with cervical cancer, clinicians should perform direct antiglobulin test (Coombs test) and indirect antiglobulin test to screen for autoimmune hemolysis. Distinguishing it from drug-induced hemolysis and myelosuppression is essential, as prompt recognition allows early initiation of corticosteroids. Future work should prioritize mechanistic research to elucidate how cervical cancer affects immune tolerance and triggers red blood cell autoimmunity.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YK and LZ conceptualized the case report, wrote the manuscript and performed additional data analysis. YK and YX were involved in the treatment and follow-up of the case. YX

critically revised the manuscript, provided supervision and approved the final manuscript for publication. All authors read and approved the final version of the manuscript. YK and YX confirm the authenticity of all raw data.

Ethics approval and consent to participate

Ethics approval was not required for the present study in accordance with local and institutional requirements. The study was conducted in accordance with local legislation and institutional requirements. The participant provided written informed consent to participate in the present study.

Patient consent for publication

Written informed consent for publication of the present article was obtained from the participant.

Competing interests

The authors declare that they have no competing interests.

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