



Oncology

Perioperative management of cold agglutinin autoimmune hemolytic anemia in an older adult undergoing radical cystectomy for bladder cancer



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ABSTRACT

Patients diagnosed with bladder cancer are most frequently older adults who have multiple chronic conditions. Frequently, new conditions are unmasked during preoperative evaluation for surgery such as radical cystectomy. We report the case of an 85 year old male with muscle invasive bladder cancer who was concurrently diagnosed with cold agglutinin hemolytic anemia. This case demonstrates the importance of close attention to underlying chronic conditions in older adults considering major cancer surgery and the need for multidisciplinary management in medically complex cases.

Introduction

Bladder cancer has the highest median age at diagnosis (73 years) of all cancer sites. Bladder cancer patients have high rates of medical complexity with prior studies suggesting a median of eight coexisting chronic conditions.¹ The standard of care for muscle-invasive bladder cancer is neoadjuvant chemotherapy followed by radical cystectomy, a major extirpative surgical procedure with high rates of complications, particularly in older adults. Pre-treatment patient evaluation frequently unmasks underlying chronic conditions in this population. Accurately diagnosing and managing coexisting chronic conditions in older adults with bladder cancer is of vital importance to optimize patient outcomes. We present the multidisciplinary management of an older adult with muscle-invasive bladder cancer who was diagnosed with cold agglutinin autoimmune hemolytic anemia (AIHA) during preoperative evaluation.

Case presentation

The patient is an 85-year-old male who presented with left flank pain and gross hematuria who was subsequently diagnosed with muscle-invasive urothelial carcinoma with squamous differentiation. Neoadjuvant chemotherapy was discussed with the patient; however, he opted to proceed directly to radical cystectomy. During preoperative clinical and laboratory evaluation, he was noted to have worsening

anemia despite resolved gross hematuria (hemoglobin decreased to 8.4 g/dL from 11.7 g/dL) as well as hyperkalemia (serum potassium of 7.0 mmol/L). He was referred to hematology for evaluation and was found to have undetectable haptoglobin, elevated reticulocyte count (4.59%), indirect bilirubin at the upper limit of normal (1.2 mg/dL), lactic acid dehydrogenase (LDH) within normal limits (225 U/L), and positive direct antiglobulin (Coombs) test with positive C3d. His peripheral blood smear demonstrated red blood cell agglutination.

These findings were consistent with autoimmune hemolytic anemia secondary to cold agglutinin disease. In light of this new diagnosis, several preventative measures were taken after consultation with hematology and anesthesiology to reduce hemolysis and need for blood transfusion during surgery. These steps included plasmapheresis the day prior to surgery, raising the temperature of the operating room to 80° Fahrenheit, warming fluids and blood prior to infusion, and application of warming devices. Postoperatively, the patient wore a warming device while in bed and all intravenous fluids were heated prior to infusion. During hospitalization, he received one blood transfusion and his hemoglobin remained stable and his potassium levels were normal. Recovery was otherwise uneventful and the patient was discharged home on postoperative day six. Final pathology showed poorly differentiated urothelial carcinoma with squamous differentiation extending into the perivesicular fat with lymph node involvement (pT3bN2Mx). Five weeks postoperatively he was seen in the emergency department for

Abbreviations: AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; LDH, lactic acid dehydrogenase; RBC, red blood cell.

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symptomatic anemia requiring a transfusion. Following this incident, hematology initiated rituximab for long-term management as he preferred to avoid recurring transfusions.

Discussion

Due to advanced age and the association between bladder cancer and smoking, older adults with bladder cancer frequently have multiple chronic medical conditions. Previously undiagnosed chronic medical conditions may be unmasked during the preoperative evaluation or pre-chemotherapy for bladder cancer. To our knowledge, no prior reports have detailed the perioperative management of AIHA due to cold agglutinin in radical cystectomy patients.

AIHA is characterized by complement mediated hemolysis of erythrocytes resulting in anemia. The two broad categories of AIHA are warm and cold antibody types. The cold antibody type, or cold agglutinin disease (CAD), is characterized by binding of the cold agglutinin monoclonal protein to erythrocytes in the setting of temperatures lower than normal core body temperature. This binding results in erythrocyte agglutination and the downstream activation of the complement cascade which results in hemolysis.² The cold agglutinin form of AIHA is particularly rare, with an estimated incidence of 1 per million and a prevalence of 16 per million. Only 25% of all AIHAs are attributable to cold agglutinin disease with a median age at diagnosis of 67 years.³ Typical laboratory findings in AIHA in general and the cold agglutinin subtype are summarized in Table 1.

Few reports exist regarding the optimal management of CAD in the perioperative setting, especially for major urologic procedures. Description of the surgical ramifications of CAD is more robust in the cardiothoracic literature due to the unique challenges of managing CAD in the setting of cardiopulmonary bypass.^{3,4} Hemolysis occurs when both titer levels of cold agglutinin are sufficiently elevated and temperature is sufficiently low. Consequently, techniques to reduce hemolysis in the perioperative period are directed in two ways: decreasing complement levels and maintaining bodily warmth. Multidisciplinary management is a critical component of perioperative management of older adults with AIHA due to CAD. Table 2 summarizes recommendations for managing CAD in the perioperative setting.

Although plasmapheresis may be used to remove the cold agglutinin antibody acutely, long-term treatment is more complex. Rituximab is the current standard for chronic management. The medication requires at least four to six weeks to reach full effect. Rituximab is a chimeric monoclonal antibody active against the B cell surface protein CD20. Binding of rituximab to CD20 results in natural killer cell mediated cell death thereby reducing the activity of B cells which would otherwise increase complement production associated with hemolysis. Although no prior studies exist regarding compromised wound healing secondary to rituximab, close consultation with hematology is recommended when considering perioperative treatment. In addition, the risks of initiating an immunosuppressive medication in the setting of known malignancy must be carefully weighed between the patient and provider.

Conclusions

Older adults with bladder cancer are frequently medically complex due to coexisting chronic conditions. Attention to detail on preoperative evaluation can unmask pre-existing, undiagnosed chronic conditions that have the potential to impact postoperative outcomes. In this older adult with bladder cancer and AIHA, a multidisciplinary approach maximized safety and improved outcomes.

Table 1

Laboratory findings associated with AIHA and cold agglutinin.

Hemolytic anemia	<ul style="list-style-type: none"> - Increased red blood cell (RBC) production <ul style="list-style-type: none"> o High reticulocyte count^a - Increased RBC destruction <ul style="list-style-type: none"> o Low haptoglobin^a o High indirect bilirubin o High lactate dehydrogenase
AIHA with cold agglutinin	<ul style="list-style-type: none"> - RBC agglutination on peripheral smear^a - Direct antiglobulin (Coombs) test <ul style="list-style-type: none"> o Positive for complement C3d^a o Often negative for IgG^a

^a Findings present in this case.

Table 2

Perioperative recommendations for management of cold agglutinin disease.

Preoperative	<ul style="list-style-type: none"> - Hematology and anesthesiology consultations - Plasmapheresis to reduce cold agglutinin titer - Encourage patient to remain warm - Check preoperative labs
Intraoperative	<ul style="list-style-type: none"> - Arrange for warmed blood products and intravenous fluids - Have cross matched blood products available - Close monitoring of patient temperature and hemoglobin - Raise operating room temperature - Use blankets and forced warm air devices - Ensure all intravenous and surgical fluids are kept warm - Transfuse warmed packed RBC as needed
Postoperative	<ul style="list-style-type: none"> - Blankets, increased ambient temperature and forced warm air devices - Ensure all IV fluids and blood products are warmed - Daily blood work: BMP, CBC, CMP, haptoglobin, and LDH - Transfuse warmed packed RBC as needed - Consider repeating plasmapheresis - Inpatient hematology consultation and close outpatient follow up

Conflicts of interest

None.

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Appendix A. Supplementary data

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References

- Garg T, Young AJ, Kost KA, et al. Burden of multiple chronic conditions among patients with urological cancer. *J Urol*. 2018;199(2):543–550.
- Berentsen S, Randen U, Tjonnfjord GE. Cold agglutinin-mediated autoimmune hemolytic anemia. *Hematol Oncol Clin N Am*. 2015;29(3):455–471.
- Barbara DW, Mauermann WJ, Neal JR, Abel MD, Schaff HV, Winters JL. Cold agglutinins in patients undergoing cardiac surgery requiring cardiopulmonary bypass. *J Thorac Cardiovasc Surg*. 2013;146(3):668–680.
- Agarwal SK, Ghosh PK, Gupta D. Cardiac surgery and cold-reactive proteins. *Ann Thorac Surg*. 1995;60(4):1143–1150.