DEPARTMENT OF THE AIR FORCE
59TH MEDICAL WING (AETC)
JOINT BASE SAN ANTONIO - LACKLAND TEXAS

5 APR 2017

MEMORANDUM FOR SGO
ATTN: CAPT ADRIAN R BERSABE

FROM: 59 MDW/SGVU

SUBJECT: Professional Presentation Approval

1. Your paper, entitled **Chronic Lymphocytic Leukemia (CLL) as an Unusual Cause of Rapid Airway Compromise** presented at/published to **Case Reports in Oncologic Medicine (Journal & Abstract)** in accordance with MDWI 41-108, has been approved and assigned local file #**17169.**

2. Pertinent biographic information (name of author(s), title, etc.) has been entered into our computer file. Please advise us (by phone or mail) that your presentation was given. At that time, we will need the date (month, day and year) along with the location of your presentation. It is important to update this information so that we can provide quality support for you, your department, and the Medical Center commander. This information is used to document the scholarly activities of our professional staff and students, which is an essential component of Wilford Hall Ambulatory Surgical Center (WHASC) internship and residency programs.

3. Please know that if you are a Graduate Health Sciences Education student and your department has told you they cannot fund your publication, the 59th Clinical Research Division may pay for your basic journal publishing charges (to include costs for tables and black and white photos). We cannot pay for reprints. If you are a 59 MDW staff member, we can forward your request for funds to the designated Wing POC at the Chief Scientist's Office, Ms. Alice Houy, office phone: 210-292-8029; email address: alice.houy.civ@mail.mil.

4. Congratulations, and thank you for your efforts and time. Your contributions are vital to the medical mission. We look forward to assisting you in your future publication/presentation efforts.

Linda Steel-Goodwin

LINDA STEEL-GOODWIN, Col, USAF, BSC
Director, Clinical Investigations & Research Support

PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS

INSTRUCTIONS

USE ONLY THE MOST CURRENT 59 MDW FORM 3039 LOCATED ON AF E-PUBLISHING

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3. Attach a copy of the 59 MDW IRB or IACUC approval letter for the research related study. If this is a technical publication/presentation, state the type (e.g. case report, QA/QI study, program evaluation study, informational report/briefing, etc.) in the "Protocol Title" box.

4. Attach a copy of your abstract, paper, poster and other supporting documentation.

5. Save and forward, via email, the processing form and all supporting documentation to your unit commander, program director or immediate supervisor for review/approval.

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    For presentations before professional societies and like organizations, the 59 MDW Public Affairs Office (PAO) will provide the needed review to ensure proper disclaimers are included and the subject matter of the presentation does not create any cause for DoD concern.

    If the sponsor of a conference or meeting is a DoD entity, an ethics review of your presentation is not required, since the DoD entity is responsible to obtain all approvals for the event.

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PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS

1. TO: CLINICAL RESEARCH	2. FROM: (Author's Name, Rank, Grade, Office Symbol)	3. GME/GHSE STUDENT:	4. PROTOCOL NUMBER
	ADRIAN R. BERSABE, CAPT., O3, SGO	☒ YES ☐ NO	N/A

5. PROTOCOL TITLE: (**NOTE:** For each new release of medical research or technical information as a publication/presentation, a new 59 MDW Form 3039 must be submitted for review and approval.)

N/A

6. TITLE OF MATERIAL TO BE PUBLISHED OR PRESENTED:

Chronic lymphocytic leukemia (CLL) as an Unusual Cause of Rapid Airway Compromise

7. FUNDING RECEIVED FOR THIS STUDY? ☐ YES ☒ NO FUNDING SOURCE:

8. DO YOU NEED FUNDING SUPPORT FOR PUBLICATION PURPOSES: ☐ YES ☒ NO

9. IS THIS MATERIAL CLASSIFIED? ☐ YES ☒ NO

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☒ 11a. PUBLICATION/JOURNAL (List intended publication/journal.)
Case Reports in Oncologic Medicine

☒ 11b. PUBLISHED ABSTRACT (List intended journal.)
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DATE	
30 March 2017	

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BERSABE, ADRIAN, R.; adrian.r.bersabe.mil@mail.mil	210-513-0759

16. AUTHORSHIP AND CO-AUTHOR(S) List in the order they will appear in the manuscript.

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d. John S. Renshaw	O5/LtCol.		59 MDW
e.			

17. IS A 502 ISG/JAC ETHICS REVIEW REQUIRED (JER DOD 5500.07-R)? ☐ YES ☐ NO

I CERTIFY ANY HUMAN OR ANIMAL RESEARCH RELATED STUDIES WERE APPROVED AND PERFORMED IN STRICT ACCORDANCE WITH 32 CFR 219, AFMAN 40-401_IP, AND 59 MDWI 41-108. I HAVE READ THE FINAL VERSION OF THE ATTACHED MATERIAL AND CERTIFY THAT IT IS AN ACCURATE MANUSCRIPT FOR PUBLICATION AND/OR PRESENTATION.

18. AUTHOR'S PRINTED NAME, RANK, GRADE	19. AUTHOR'S SIGNATURE	20. DATE
Adrian R. Bersabe, Capt., O3	BERSABE.ADRIAN.R.1176528180	21 March 2017

21. APPROVING AUTHORITY'S PRINTED NAME, RANK, TITLE	22. APPROVING AUTHORITY'S SIGNATURE	23. DATE
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TO: Clinical Research Division 59 MDW/CRD Contact 292-7141 for email instructions.	24. DATE RECEIVED 4 APR 2017	25. ASSIGNED PROCESSING REQUEST FILE NUMBER 17169

26. DATE REVIEWED	27. DATE FORWARDED TO 502 ISG/JAC
5 April 2017	

28. AUTHOR CONTACTED FOR RECOMMENDED OR NECESSARY CHANGES: ☑ NO ☐ YES If yes, give date. _____ ☐ N/A

29. COMMENTS ☑ APPROVED ☐ DISAPPROVED

Single subject case study with appropriate disclaimers. Approved

30. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER	31. REVIEWER SIGNATURE	32. DATE
Kevin Kupferer/GS13/Hum Res Subj Prot Expert	KUPFERER.KEVIN.R.1086667270 Digitally signed by KUPFERER.KEVIN.R.1086667270 DN: c=US, o=U.S. Government, ou=DoD, ou=PKI, ou=USAF, cn=KUPFERER.KEVIN.R.1086667270 Date: 2017.04.05 06:41:29 -05'00'	5 April 2017

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April 5, 2017	April 5, 2017

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42. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER	43. REVIEWER SIGNATURE	44. DATE
Kevin Iinuma, SSgt/E-5, 59 MDW Public Affairs	IINUMA.KEVIN.MITSUGU.1296227613 Digitally signed by IINUMA.KEVIN.MITSUGU.1296227613 DN: c=US, o=U.S. Government, ou=DoD, ou=PKI, ou=USAF, cn=IINUMA.KEVIN.MITSUGU.1296227613 Date: 2017.04.05 12:30:32 -05'00'	April 5, 2017

4th ENDORSEMENT (59 MDW/SGVU Use Only)

45. DATE RECEIVED	46. SENIOR AUTHOR NOTIFIED BY PHONE OF APPROVAL OR DISAPPROVAL ☐ YES ☐ NO ☐ COULD NOT BE REACHED ☐ LEFT MESSAGE

47. COMMENTS ☐ APPROVED ☐ DISAPPROVED

48. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER	49. REVIEWER SIGNATURE	50. DATE

Title: Chronic lymphocytic leukemia (CLL) as an Unusual Cause of Rapid Airway Compromise

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Abstract:

Chronic Lymphocytic Leukemia (CLL) is the most prevalent form of non-Hodgkin's lymphoma (NHL) in Western countries predominantly affecting adults over age 65. CLL is commonly indolent in nature but can present locally and aggressively at extranodal sites. Although CLL may commonly present with cervical lymphadenopathy, manifestations in non-lymphoid regions of the head and neck is not well-described. CLL causing upper airway obstruction is even more uncommon. We describe a case of a patient with known history of CLL and stable lymphocytosis that developed an enlarging lymphoid base of tongue (BOT) mass resulting in rapid airway compromise.

Introduction:

Chronic Lymphocytic Leukemia (CLL) is the most common form of adult Non-Hodgkin's Lymphoma (NHL). This mature B-cell neoplasm has an incidence rate of 4.6 per 100,000 people in the United States each year [1, 2, 3, 4, 5]. This disease process predominantly affects adults over age 65 and is more common in men. CLL has an extremely variable course of presentation ranging from asymptomatic lymphocytosis to painless lymphadenopathy, hepatomegaly, splenomegaly, cytopenias, and infections. Patients may also present with the typical "B" symptoms of unintentional weight loss, fever, and drenching night sweats [3, 4, 5]. Rapid progression with transformation into an aggressive, high-grade NHL is known as Richter syndrome and may occur in up to 10% of patients with CLL [6].

Although indolent in nature, CLL can present as locally aggressive extranodal mass resulting in symptoms depending on the location and extent of tissue involvement [7]. We present a unique case of a patient with known CLL and stable lymphocytosis for many years that later developed rapid airway compromise from an enlarging lymphoid base of tongue (BOT) mass which was identified as non-transformed CLL.

Case Presentation:

A 62-year-old woman with untreated Rai stage II CLL was initially diagnosed in January 2007. At that time she was found to have an absolute lymphocyte count (ALC) of 8 g/dL, mild splenomegaly, and mild abdominal lymphadenopathy. She was otherwise asymptomatic. Bone marrow biopsy confirmed a monoclonal B-cell population of lymphocytes with CD5 and dim CD23 co-expression. Results at that time also showed normal cytogenetics, FISH negative for 11q deletion, 13q deletion, p53 deletion and trisomy 12. β-2 microglobin was 2.4 mg/L and ZAP 70 was normal. She underwent close observation for several years. During this period of surveillance, she did not experience any recurrent bacterial infections, and serial monitoring of quantitative immunoglobulins demonstrated IgG levels greater than 500mg/dL.

However, in December 2011, she presented to the emergency department for complaints of feeling a globus sensation over the span of forty-eight hours. This symptom was associated with dysphagia, diffuse myalgias, high-grade fevers, and shortness of breath. ALC at the time remained stable at 8.5 g/dL with no evidence of anemia or thrombocytopenia. Lactate dehydrogenase (LDH) was normal at 188 IU/L and β-2 microglobin was elevated to 3.3 mg/L. CT scan of the neck demonstrated a large heterogeneously enhancing 4.1cm mass involving the palatine tonsils causing severe narrowing of the hypopharynx. She was admitted and quickly developed worsening shortness of breath and stridor prompting otolaryngology consultation for urgent tracheostomy placement.

The BOT mass was biopsied at the time of tracheostomy placement. The pathology specimen demonstrated squamous mucosa with acute inflammation and reactive hyperplasia most consistent with bacterial infection and lymphoid tissue hyper-reactivity. No monoclonal lymphocyte population was identified. Furthermore, no pathogens were isolated from biopsy specimen, blood cultures, or

sputum cultures, and CRP was normal at 0.06 mg/dL. However, the decision was made to empirically treat with ten days of moxifloxacin. After completing her course of antibiotics, she noted complete resolution of her globus sensation, dysphagia, fevers, and myalgias.

Although her symptoms had completely resolved, a CT of the neck was repeated and showed persistence of the BOT mass six weeks after her initial admission for rapid airway compromise. Direct laryngoscopy was thus performed, and repeat biopsy of the mass now showed a monomorphic population of CD20+, CD5+, CD23+, and cyclin D1 negative lymphocytes consistent with patient's previous diagnosis of CLL (Fig. 1). PET-CT to evaluate for other sites of disease showed FDG-avid lingular tonsillar irregularity and hypertrophy (SUV of 4.9, mediastinal blood pool activity with SUV of 1.5) with numerous sub-centimeter cervical lymph nodes that were only mildly FDG-avid (maximum SUV of 2.2). There was no other evidence of lymphadenopathy, and the spleen was not significantly enlarged. Given the patient's initial presentation with rapid deterioration resulting in respiratory failure, Richter transformation was considered. Again, however, biopsy results did reveal transformation into a more aggressive NHL clone, and PET-CT showed localized disease which both argue against this phenomenon, however.

Fig 1:

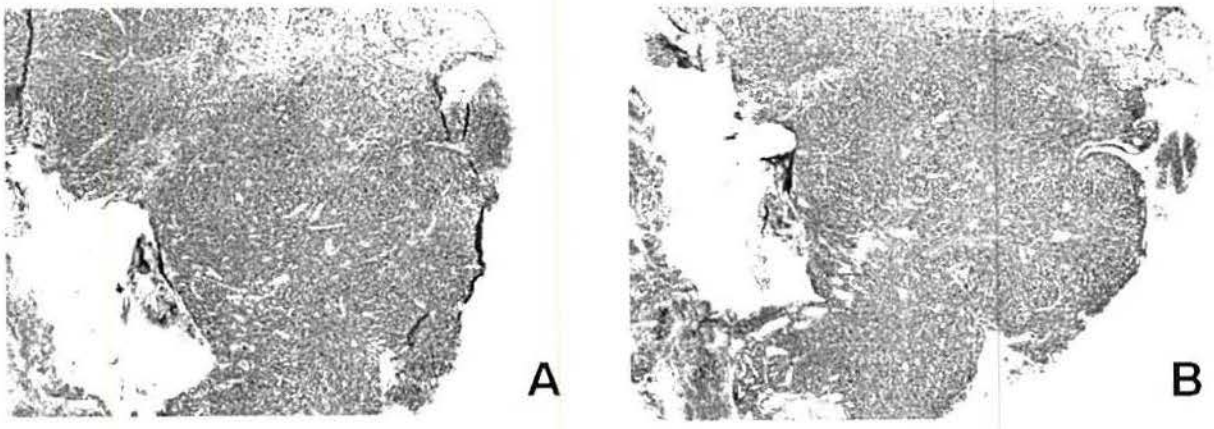

Fig 1. Immunohistochemical staining demonstrating a monomorphic population of CD20 positive lymphocytes with co-expression of CD5 typical of CLL.

She was started on chemotherapy with bendamustine and rituximab (BR) with a dramatic anatomic response after two cycles (Fig. 2) and near complete response (CR) after four cycles when tracheostomy was removed. She eventually completed 6 cycles of BR in October 2012 and achieved a CR with complete marrow recovery confirmed by bone marrow biopsy. She has been closely followed in the outpatient setting with no evidence of disease recurrence as of March 2017.

Fig 2:

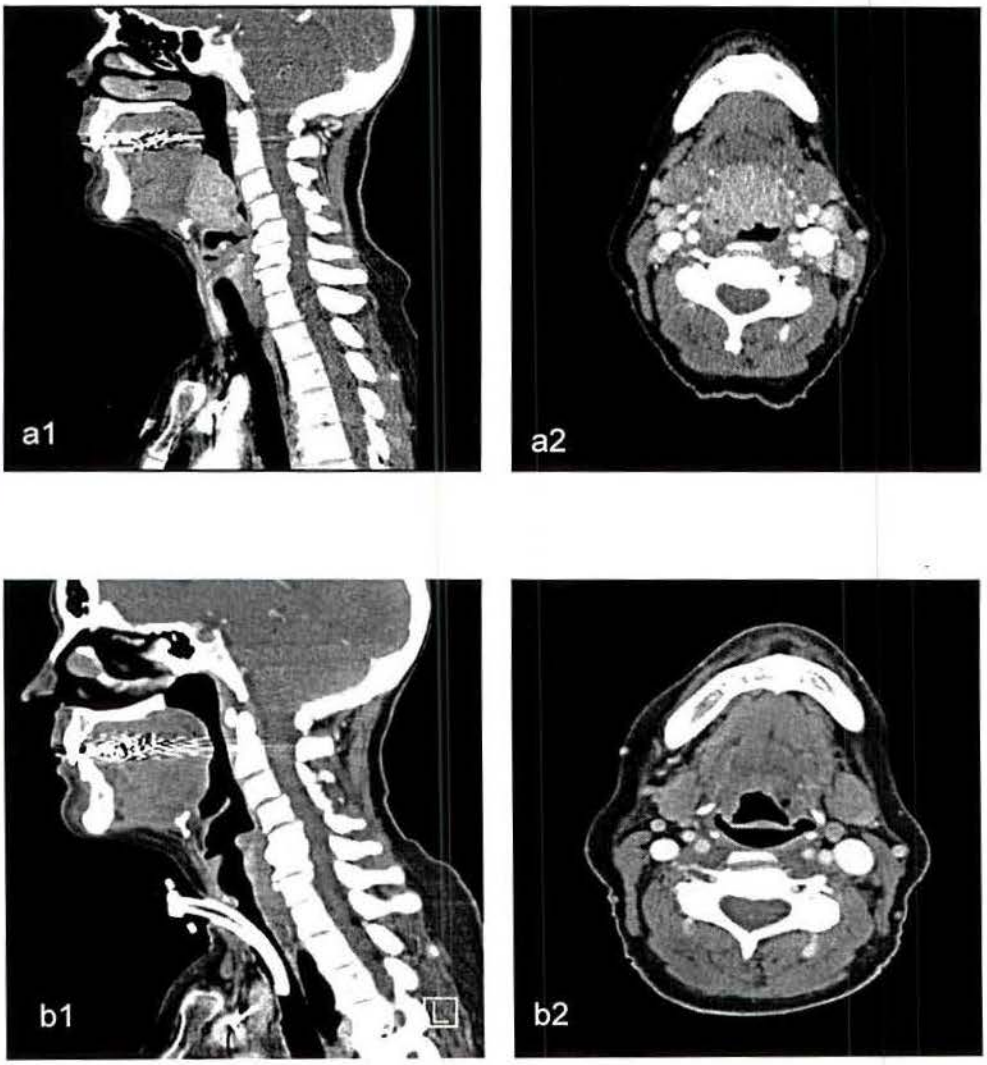

Fig 2. Interval change in size of BOT mass on contrasted CT scan of the head and neck before (a1 and a2) and after (b1 and b2) two cycles of Bendamustine and Rituximab.

Discussion:

Current literature regarding the presentation of CLL of the head and neck is very limited [5]. Although lymphomas often present in Waldeyer's ring of the pharynx, involvement of the oral cavity, larynx, and hypopharynx is exceedingly uncommon [7]. A rare case of palatal infiltration has been described by Vibhute, et al. When lymphomas present in the oral cavity, some more common manifestations include gingival hypertrophy, petechial hemorrhage or ecchymosis, infection, ulceration and necrosis [8]. Most presentations of CLL of the head and neck manifest as cervical lymphadenopathy or skin involvement, with the latter predicting poor prognosis [5, 8].

Upper airway obstruction resulting from CLL is even more uncommon. Although rare, airway obstruction is more often the result of mass effect from hilar and mediastinal adenopathy [4]. More common malignant causes of upper airway obstruction include locally advanced lung cancer as well as metastases from thyroid, skin, head and neck, or breast cancer [7, 9]. Regardless of the exact etiology, the approach to malignant airway obstruction is variable across different clinicians and institutions and may involve single or multi-modality therapies [9].

The possibility of Richter syndrome with transformation of CLL into a large cell lymphoma was indeed entertained after it was later discovered that the underlying etiology of the patient's respiratory decline was due to CLL. Richter transformation can occur in 3 to 10% of patients with CLL. Underlying infections have also been implicated in triggering these transformations [6]. Although it is still debated, it is theorized that the Epstein-Barr virus (EBV) has a role in Richter transformation through direct oncogenic stimulation or through mitogenic and activating signals within the microenvironment. Rapid clinical deterioration is often a hallmark of Richter transformation similar to the presentation of our patient. The usual presentation of this aggressive transformation often includes increasing

lymphocytosis, progressive cytopenias, elevated LDH, and sometimes diffuse, bulky lymphadenopathy [11]. Other than rapid respiratory decline, our patient did not have any of these findings, and a repeat biopsy result confirmed CLL.

Another clinical challenge faced in this particular case was the presentation of a likely overlying infection given acuity of onset, fevers, and initial biopsy denoting acute inflammation and reactive lymphoid hyperplasia with a lack of monoclonal B-cell population. Infections are indeed the leading cause of death in patients with CLL and can account for up to 60% of disease-related mortality. This is due to a constellation of immune defects involving T-cell dysfunction, reduced complement levels, hypogammaglobulinemia, and impaired B-cell function [11]. A superimposed infection could not be ruled out in this case, given the initial presentation with acute inflammatory changes and lymphoid hyperplasia on biopsy and clinical improvement with antibiotics. In fact, Salem *et al.* describes four cases of patient with CLL who presenting with B-symptoms and laboratory and imaging findings concerning for progression of their lymphoma but were instead found to have a superimposed Herpes simplex viral infection. Our patient presenting symptoms concerning for an underlying infection, but biopsy and microbiology work-up did not reveal a definitive pathogen.

CLL and other indolent extranodal lymphomas (ENL) are highly responsive to systemic therapy. For this reason, systemic therapy is considered the primary treatment modality for aggressive, localized ENL, unless they are considered unfit for or refuse such treatment. The treatment regimen of Bendamustine and Rituximab was chosen in this case due to high response rates and favorable safety profile [3]. However, low-dose radiation therapy is highly effective and may be considered for patients with stage IIIE/IV disease for palliative intent [7].

In summary, this case illustrates an unusual presentation of CLL causing airway compromise in a patient with a non-transformed indolent lymphoma. Prompt recognition is required to institute early

intervention. Initial biopsy findings were concerning for a possible bacterial infection in this patient with known CLL. However, the a superimposed bacterial infection may have complicated the clinical picture. Nevertheless, cases of infection mimicking CLL progression have been described and accurate identification of the underlying etiology is essential in order to make appropriate treatment decisions. This patient responded very well and achieved a CR after completing six cycles of BR. She has maintained a CR for over four years after completing cytotoxic therapy.

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Competing Interests:

No competing financial or non-financial interests exist in the preparation of this manuscript.

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