# Hairy Cell Leukemia and Ground Water Contamination With Industrial Solvents: a Case Report

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**ABSTRACT** The industrial solvents benzene and trichloroethylene (TCE) are known carcinogens, and these solvents contaminated the drinking water at Marine Corps Base Camp Lejeune from the 1950s to 1980s. Benzene and TCE are linked to the hematopoietic cancers acute myelocytic and lymphocytic leukemia and chronic lymphocytic leukemia. We report the case of a veteran stationed at Marine Corps Base Camp Lejeune during this period who developed hairy cell leukemia (HCL), a rare form of lymphocytic leukemia. We review his presentation, medical history, solvent exposure, and literature on the carcinogenicity of benzene and TCE. This patient represents a possible link of TCE or benzene to HCL. The case also informs clinicians of the updated epidemiology with regards to clinical findings for HCL.

## INTRODUCTION

Hairy cell leukemia (HCL) is an uncommon indolent malignancy of B cells that accounts for 2% of all leukemias.[1,2] Clonal B-cell lymphocytes develop BRAF-V600E kinase-activating mutations that cause rearrangements of immunoglobulin genes that infiltrate the reticuloendothelial system. HCL has a classical presentation of pancytopenia, aplastic anemia, large mononuclear cells with cytoplasmic projections, and splenomegaly.[2] Etiology is unclear, though suggestions include occupational and environmental exposures.

The carcinogenicity of several industrial solvents, including such solvents benzene and trichloroethylene (TCE), was assessed and published in 2012 and 2017 by the International Agency for Research on Cancer (IARC). Benzene and TCE demonstrate sufficient evidence in humans and animals demonstrate carcinogens.[3,4] Human exposure to these solvents is primarily via water sources and in occupations, including dry cleaning, metalworking, and construction.

### *Objective*

The purpose of this paper is to report a possible link of industrial solvents or benzene to hematopoietic cancers, specifically HCL, and inform clinicians of the updated epidemiology with regards to clinical findings for HCL.

### *Case Presentation*

The patient is a 59-year-old male veteran with a history of type II diabetes mellitus, hypertension, and a current smoker presenting to establish care. He reported 3 months of fevers, chills, drenching night sweats, general malaise, and fatigue. The patient's medical exposure history for smoking is significant for being a current smoker at ½ pack a day with a 40 pack-year. He also served in the military at Marine Corps Base Camp Lejeune for 5 years in the 1970s. He denied work on farms, with pesticides or petroleum products, and radiation work.

On physical exam, vital signs were normal with no hepatosplenomegaly or lymphadenopathy. Labs revealed pancytopenia with a leukocyte count of 1.3 K/cmm (normal 3.2–9.5 K/cmm), hemoglobin of 10.7 g/dL (normal 13.2–17.3 g/dl), and platelets of 131 (normal 152–375 K/cmm). Peripheral blood showed pancytopenia, including monocytopenia and lymphopenia, rare small mature lymphocytes, and no hairy cells. Computed tomography was also negative for lymphadenopathy and hepatosplenomegaly (Fig. 1).

Bone marrow core and aspirate were hypercellular with markedly suppressed trilineage hematopoiesis, and diffuse lymphoid infiltrate consisting of small to medium-sized lymphocytes with abundant cytoplasm, oval to indented nuclei, and homogenous chromatin. Immunohistochemical stains revealed predominantly CD20 and Pax5 positive B-cells co-expressing cyclin D1 and tartrate-resistant acid phosphatase (TRAP) (Fig. 2). They were negative for CD3, CD5, CD10, CD123, and annexin A1. Flow cytometry analysis demonstrated monoclonal B cells that were positive for CD19, CD20, CD22, CD11C, CD25, CD103, λ light chain, and negative for CD5, CD10, and $\kappa$ light chain. Cytogenetic study shows normal male karyotype 46, XY. FISH analysis revealed gains of chromosome 5 and PCR analysis positive for BRAF V600E.

The patient's flow cytometry and immunophenotyping were consistent with HCL.[5] Consistent findings include pan-B-cell antigens, such as CD19, CD20, and CD22. Cells also stain positive for TRAP. First-line therapies are pentostatin

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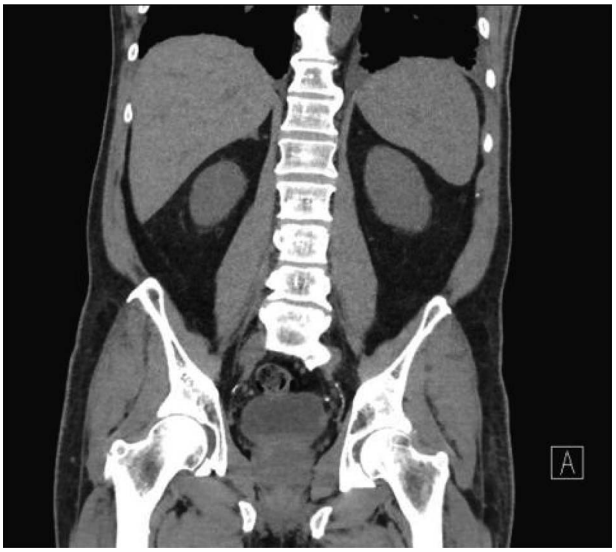


**FIGURE 1.** Computed tomography imaging of patient showing an unremarkable spleen and liver.

and cladribine. The patient's treatment with precision therapy using cladribine yielded a good response. He has not required treatment for relapsed disease with moxetumomab, vemurafenib, and rituximab or ibrutinib.

## DISCUSSION

HCL has a median age of onset of 55 years and is three to four times more likely in males.[1,2] Genetics appears to have a little role in the disease.[1] There are very few cases of familial HCL described in the literature, and in those cases, it is unclear whether genetics or similar environments were responsible. Otherwise, HCL has a higher incidence among Caucasians and lower incidence among Asians, Africans, and Arabs.[1,6,7] The disease classically presents with splenomegaly and hypocellular bone marrow on aspirate. His lack of splenomegaly is becoming more common owing to early diagnosis with hematologic studies.[2] Peripheral lymphadenopathy is uncommon, and abdominal lymphadenopathy correlates with duration of disease.[2] Atypically, this patient has a considerable tobacco history of 40 pack-years, and HCL has an inverse relationship with smoking.[1]

Occupational and environmental risk factors with regards to HCL are still unclear. There is a possible increase in the risk of HCL in exposure to cattle farms, pesticides, petroleum products, and ionizing radiation.[1] Our patient's history was negative for these exposures, though he reported a work history as a plumber. He denied exposure to industrial solvents in his workplace. B-cell malignancies as a whole are linked with exposure to pesticides, herbicides, and organic chemicals. This patient's military service includes 5 years of service at Marine Corps Base Camp Lejeune. The industrial solvents TCE, tetrachloroethylene (PCE), *trans*-1,2 dichloroethylene, and benzene contaminated Camp Lejeune's drinking water, from the 1950s to 1980s. TCE and PCE were the primary contaminants, with levels ~215 mg/L and 1400 mg/L measured in the two contaminated water sources from 1975 to 1985,

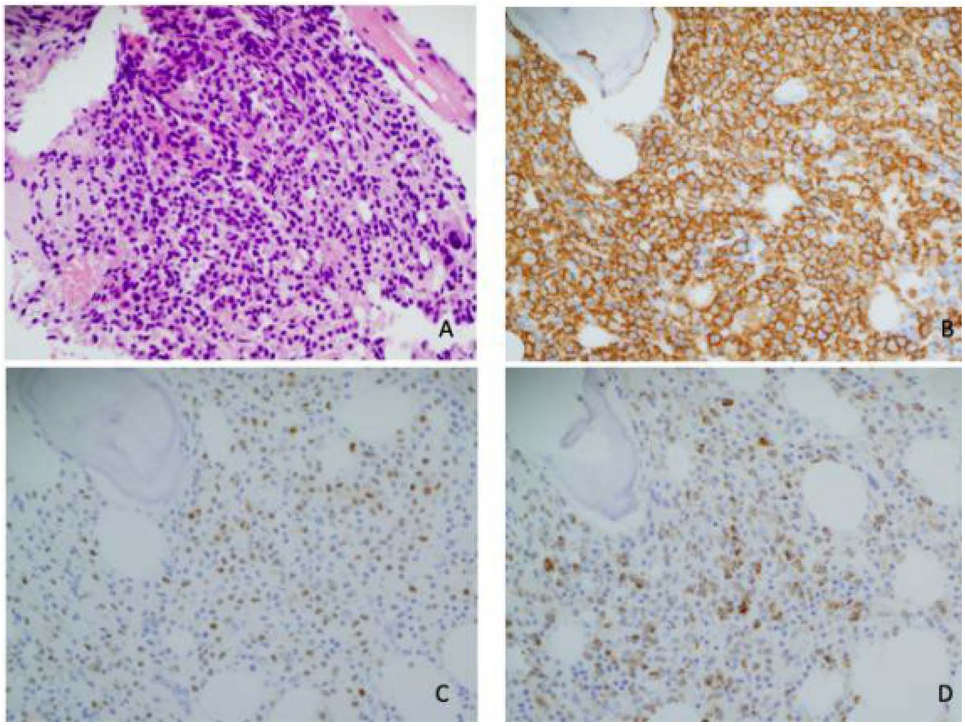


**FIGURE 2.** Bone marrow biopsy showing hypercellular marrow with diffuse lymphoid infiltrates (A, hematoxylin and eosin, ×400) consisting of predominant B cells that are positive for CD20 (B, ×400), cyclin D1 (C, ×400) and TRAP (D, ×400).

respectively. Maximum U.S. contaminant levels are 5 mg/L for TCE, PCE, and benzene. Lower levels of benzene and *trans*-1,2 dichloroethylene were present at smaller levels as breakdown products of the former.[8]

TCE and benzene are carcinogens, while PCE is classified as "likely carcinogenic," and the cancer classification of *trans*-1,2 dichloroethylene is not currently available. As in our patient, human exposure typically occurs through contaminated drinking water and food. As previously mentioned, the IARC assessed the carcinogenicity of several chlorinated solvents in 2012 in humans and animals.[4] Chlorinated solvents act as a carcinogen via the production of oxidative metabolites that are genotoxic. Animal studies demonstrate an association with TCE and an increased incidence of hemopoietic tumors.[4] Other malignancies implicated in these industrial solvent exposures include kidney, bladder, and liver cancers.[4] In 2017, the IARC finalized an evaluation of the carcinogenicity of benzene. Benzene is a known cause of acute myelocytic leukemia and acute lymphocytic leukemia.[3] Benzene acts as a carcinogen via oxidative stress that, in turn, directly damages DNA, resulting in aberrant replication. A case-cohort in 2015 also demonstrates causation between benzene exposure and chronic lymphocytic leukemia in offshore oil industry workers.[9]

Despite benzene and TCE's known carcinogenicity, there is no known link between HCL and these solvents. A single study of the affected Camp Lejeune population showed an increased incidence of leukemia.[8] This information, however, is extracted from death certificates of the residents, and there were no HCL codes in the data.[8] Of note, this study showed a hazard ratio for hematopoietic cancers of 1.05 with upper confidence limit, lower confidence limit, and *P*-values of 0.82, 1.33, and 0.57, respectively.[8] More recent studies show declines in B cells with exposure to benzene and TCE.[10]

## CONCLUSION

HCL is an uncommon indolent B-cell malignancy with possible exposure links to cattle farms, pesticides, petroleum products, and ionizing radiation. There is no known link between HCL and industrial solvents, but data on this topic are sparse. This case of a veteran with HCL exposed to drinking water contaminated with these solvents presents a possible link. Further study is needed to determine environmental and occupational exposure risk factors in HCL.

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