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(CASE REPORT)

Incidental skin manifestation of trisomy 12 chronic lymphocytic leukemia

Kenneth Rodrigues [1,*], Derek Oh [1], Blerina Asllanaj [1] and Ann Wierman [2]

[1] *Department of Internal Medicine, HCA Healthcare; Mountain View Hospital, Las Vegas, NV, USA.*
[2] *Department of Hematology and Oncology, HCA Healthcare; Mountain View Hospital, Las Vegas, NV, USA.*

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Abstract

Chronic lymphocytic leukemia (CLL) is one of the most prevalent B-cell cancers for people over the age of 65. CLL is commonly comorbid with trisomy 12, as reported in up to 20% of cases. In our case, trisomy 12 was incidentally found on this patient. Its pathophysiology is quite unclear but has played a role in the side effect profile of CLL. Trisomy 12 with CLL has been shown to have increased risk for side effects like thrombocytopenia, Richter transformation and hematological cancers. The goal of this case presentation is to discuss a case of CLL with cutaneous manifestations and to look at the role that trisomy 12 can play.

Keywords: Chronic lymphocytic leukemia; Trisomy 12; CD5 B-cell; Flow cytometry; Leukemia cutis

1. Introduction

Chronic lymphocytic leukemia (CLL) is a common cancer in the western world and is the most common leukemia overall [1]. CLL is based on neoplastic proliferation of B cells in the bone marrow. This disease is mainly diagnosed in older adults, like our patient. Often affecting Caucasians at a higher percentage compared to the general population. Frequently at presentation, patients are asymptomatic, with only lymphocytosis on laboratory testing. Some of the common manifestations are lymphadenopathy, hepatomegaly and splenomegaly along with fever and malaise. Initial testing usually results from a complete blood count showing lymphocyte counts more than 5000mcL [1]. Peripheral smear can show smudge cells which are remnants of leukocytes lacking cytoplasm. This is due to irregular fragility in the leukocytes. Flow cytometry is used in diagnosis, with some common markers including CD5, CD19, CD 20, and CD 23 marker [1]. CD5 B-cells marker are a hallmark for the disease, being expressed in above 90% of patients with CLL [2]. Trisomy 12 is commonly comorbid with CLL but it's unclear its pathophysiology and true impact. It is ultimately the second most common chromosomal abnormalities [3]. It usually is discovered at diagnosis with fluorescence in situ hybridization [3]. Bone marrow biopsy is generally not required for diagnosis of CLL and is used mostly for staging along with PET/CT.

For our patient, he presented with cutaneous manifestations of CLL, which can occur in 25% of CLL patients [4]. These manifestations of the skin in leukemia patients are often described as leukemia cutis. Generally, leukemia is more associated with findings in the blood, bone marrow, spleen and lymph nodes but skin findings are possible and often under reported [5]. This can occur with cancer cells infiltrating the skin giving lesions, plaques or abnormal skin findings. The most commonly skin finding is papulonodular skin lesions [6]. Head, neck, earlobe, truck and extremities are the most common sites of these manifestations [6]. There is minimal studies or findings on prognosis and treatment effective for skin manifestations of CLL. This case looks to present correlation between trisomy 12 and skin manifestation of CLL.

* Corresponding author: Kenneth Rodrigues

2. Case Presentation

A 55-year-old male with a history of type 2 diabetes mellitus presented to the emergency department (ED) after a motor vehicle accident in 2016. Patient had minor injuries to left lower chest, left thigh and lip. Initial laboratory values revealed blood sugar of 600 mmol/L. Patient was found to not be in diabetic ketoacidosis. He was reported to be a very experienced driver of motorcycles and stated he crashed due to getting disoriented prior to his accident. At that time, chest x-ray was completed which did not show any acute pathology. He next underwent a left femur x-ray which did not show any lytic or blastic lesions or any acute fractures. While in ED, patient received a liter of 0.9% normal saline and 10 units of insulin. He had sutures placed in his lip due to laceration and patient was discharged to home that same day. He was referred to endocrinology who would recommend the patient start on glargine insulin 10 units, as his sugars were ranging from 400-600 mmol/L.

Upon further evaluation, white blood cell count was noted to be elevated 28.5 x10^9/L. Patient was subsequently admitted to the hospital for further evaluation. He reported recent subjective fever, nonintentional weight loss and night sweats. Labs showed, hemoglobin, hematocrit, haptoglobin, reticulocyte count, LDH, electrolytes, creatine, hepatitis panel, HIV panel were all without abnormality. Patient did have hypogammaglobinemia found on laboratory studies. Computed tomography (CT) of abdomen and pelvis with contrast showed splenomegaly and enlarged mesenteric and retroperitoneal lymph nodes. CT of chest showed multiple small calcified hilar and mediastinal lymph nodes along with small sub-centimeter axillary nodes and supraclavicular nodes. No lymph nodes were described as pathologic in appearance. A Wright-Giesma stained peripheral blood smear showed significant leukocytosis with smudge cells apparent. Patient underwent flow cytometry. Flow cytometric immunophenotyping showed an increased population of monotypic lymphocytes (approximately 45% of the total cells) expressing CD5, CD19, dim-CD20, CD23, CD52, HLA-DR, and FMC-7 with kappa surface light chain restriction. This population was negative for CD10 and CD38. These finding were consistent with B cell non Hodgkin's lymphoma and possible CLL. Patient underwent bone marrow biopsy to help with staging. Sample was taken from the right illac crest. During cytogenic analysis, this patient was found to have a trisomy of chromosome 12 which is common in patients with CLL. Fluorescence in situ hybridization (FISH) analysis was performed on this patient's specimen using DNA probes for a CLL panel. Two hundred interphase nuclei were examined for each probe and the signal patterns revealed the following: Positive for trisomy of chromosome 12 (69.5% of nuclei). IgVH Somatic Hypermutation Analysis was not completed due to insufficient quality or quantity of RNA obtained for analysis in this specimen. Core biopsy showed uniform cellularity, large interstitial infiltrate of lymphoid cells and many B cells along with no signs of fibrosis. Patient was discharged to with follow up to hematology and oncology in regards to management in 2016.

Patient has continued to follow with Hematology-Oncology team during this time until 2022. In 2022, patient was referred to the dermatologist for follow-up. Patient had a history of malignant melanoma on his face and was removed by excisional biopsy in 2019. Along with history of basal cell and squamous cell carcinomas on face and left anterior shoulder. Patient had been experiencing a pruritic mass on his right arm going on for several months prior to referral to the dermatologist. Patient was well-appearing and without acute distress on examination. The mass was described as well-defined and mobile with hyperpigmentation. Mass was 1.9 cm in diameter. At this time, patient was referred to general surgery for biopsy of the mass and to follow-up as needed in regards to his management. Patient was told that it would be likely a lipoma. A sample was obtained by biopsy which was sized at 0.5x0.5x0.4cm (Figure 1). Stained sectioning of the sample showed sheet like lymphoid tissue composed small to medium sized lymphocytes with sclerotic intervening stroma, likely showing lymph tissue. Immunohistochemical profile showed CD3, CD5, Bcl-6 to be lymphocytic positive, CD 20, bcl-2, CD 23 to be lymphocytic positive, CD10, cyclin D1 to be predominantly lymphocytic negative. KI 67 was stated have an increased proliferative index completed by a pathology team at the local Veterans Affairs Hospital. Pathology report stated that these manifestations were most likely from a skin finding of CLL. Patient underwent IGH gene reassessment by PCR which showed the finding to be monoclonal, supporting the diagnosis of a b-cell lymphoma.

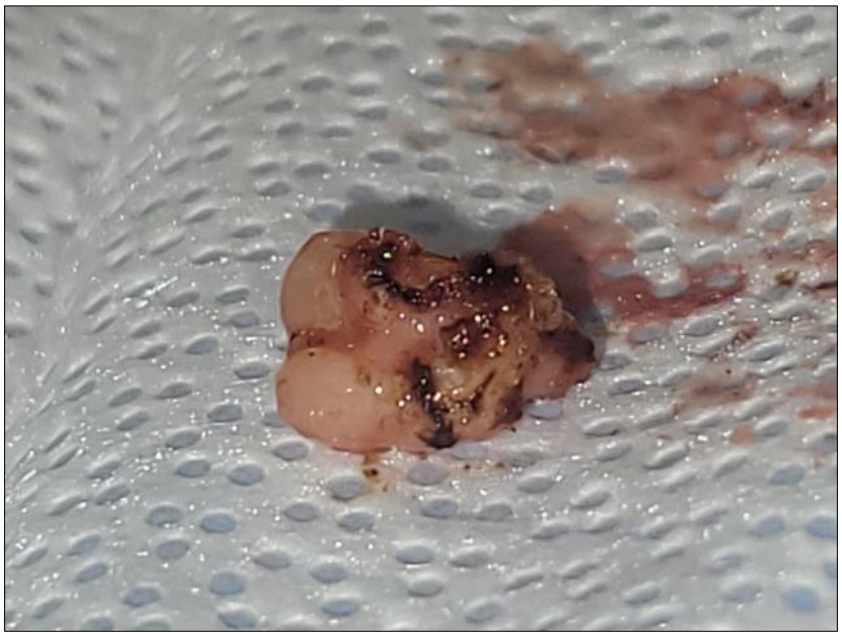

Figure 1 A 0.5x0.5x0.4cm mass extracted from patient's arm

3. Discussion

Although a predisposition related to familial inheritance has long been understood to play a significant role in the development of CLL, elucidation of the precise genetic means of pathogenesis is yet to be determined [7]. Numerous clues, however, are apparent. CLL is known to be a condition predominantly of people of European descent, with considerably lower rates among Asians – a relationship that is preserved among Asian people who have immigrated, suggesting a chiefly genetic basis for disease [8]. Furthermore, CLL is notable for its heterogeneity, with clinical courses ranging from long survival periods without the need for intervention to aggression marked by rapid progression [9]. Altogether, the general patterns and variations in CLL epidemiology and presentation suggest multiple genetic bases and mechanisms from which disease may arise. For our patient, trisomy 12 was a relevant genetic finding which was incur specific complications in CLL patients.

We described the incidental detection of CLL and trisomy 12 in this case presentation. Trisomy 12 and CLL constitutes a more mysterious variant of the disease, and few investigations have sought to further describe its aberrant pathways [10]. It is marked by both indolent and more aggressive courses, with each type of progression of disease marked by differences in IGF1R expression, IGHV mutation, and NOTCH4 status, among others [3]. Although our patient's clinical course was notable for B symptoms, including fever, weight loss, and night sweats, inability to follow through with genomic analyses regrettably made it difficult to further describe his prognosis status. Although CLL in general is known to be more common in people with first-degree relative CLL patients, there remains a sizable portion of patients with the sporadic variant. Our patient had no known family history of any malignancies. These variations in presentations and discrepancies in patterns highlight the continued need for medical professionals to encourage patients to seek advanced care for persistent abnormalities and to regularly follow up with their providers for general scheduled surveillance.

The correlation seen in our patient is his cutaneous manifestation IE his "lipoma" found on his arm. It is unclear, if trisomy 12 and CLL in combination has increased risk of skin manifestations for patients. Trisomy 12 is been shown to have increased risk for most clinical manifestations like Richter's transformation. Literature review on the topic did not show any specific findings on whether trisomy 12 leads to an increased risk for skin manifestations in patients with CLL. One French study did a genetic analysis of a cohort with CLL and leukemia cutis. This was the largest cohort to date. The finding showed via Fluorescence in situ hybridization (FISH) analysis that 10 out of 32 patients (31%) in the cohort had a trisomy 12 genetic mutation [5]. This study did not have any data in regards to how treatment of trisomy 12 and CLL with acute leukemia cutis fared [5]. Most patients actually had cutaneous manifestations prior to their initial treatment for CLL in 62.5%[5]. Cutaneous manifestations generally are not seen to have a poor prognosis unlike trisomy 12 which is generally been associated with higher complication rates [11]. Standard CLL treatment is usually described as adequate in responses to leukemia cutis but it is truly unclear as there are minimal studies to support this data [5].

Trisomy 12 on the other hand has been shown to have an intermediate risk in prognosis [3]. This intermediate risk prognosis is not nearly as poor as in 17q or 11 q deletions in CLL patients but does still carries a decreased median survival time[12]. Even with increased risk, treatment plans for trisomy 12 and CLL are uncertain [12]. There are no clear guidelines in terms of this treatment.

4. Conclusion

CLL constitutes a myriad of subtypes, each with varying pathogeneses, clinical phenotypes, genomic analyses, and prognoses. It is marked by both indolent courses requiring minimal intervention, if any, and rapid progression like Richter's transformations. This case showed this unique configuration of trisomy 12 and leukemia cutis in combination in a CLL patient. Guidance is truly unclear in this area and patients are often treated the same as general CLL patients. Prognosis is generally poor with patients with trisomy 12 and patients with leukemia cutis have not really been shown any clear difference in prognosis. As investigations continue to characterize CLL in its numerous forms, medical providers must remain vigilant on behalf of patients in order to ensure the most optimal outcomes possible.

Compliance with ethical standards

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Disclosure of conflict of interest

The above listed authors have no conflicts of interest to declare.

Statement of ethical approval

The present research work does not contain any studies performed on animals/humans subjects by any of the authors.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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