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Case Report

A unique presentation of an osteolytic chronic lymphocytic leukemia/small lymphocytic lymphoma as a helmet-shaped tumor

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ABSTRACT

Background: Cranial vault lymphomas (CVLs) are rare skull lesions, mostly caused by diffuse large B-cell lymphoma, a subtype of non-Hodgkin lymphoma (NHL). Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) extremely rarely causes cranial vault lesions. Herein, we report a case of a CLL/SLL causing a unique and extensive cranial vault lesion with a striking presentation of a helmet-shaped tumor, whose treatment with ibrutinib led to full bone regeneration.

Case Description: A 63-year-old woman was admitted to our hospital for the continuation of treatment of CLL/SLL, which presented with hypercalcemia, generalized lymphadenopathy, and osteolytic lesions of Th10, Th11, and L2 vertebrae. An initial head computed tomography (CT) scan, performed due to psychomotor impairment, showed an extensive CVL. Despite therapy, a control CT scan showed progression of the CVL-shaped like a helmet, destroying the occipital, both parietal and a part of the frontal bone, with the effacement of the external table and somewhat preserved internal table. Successful therapy with ibrutinib led to full bone regeneration.

Conclusion: Striking CVL presentations like the extensive permeative dissolution of the whole cranium rarely occur, especially in otherwise indolent types of NHL. Nevertheless, full bone regeneration and recovery are possible with modern treatment options, given adequate analysis is obtained beforehand. In case of a discrepancy between core-needle biopsy or fine-needle aspiration findings and the clinical picture, a surgical biopsy is warranted.

Keywords: Chronic lymphocytic leukemia/small lymphocytic lymphoma, Cranial vault lymphoma, Ibrutinib, Non-Hodgkin lymphoma

INTRODUCTION

Cranial vault tumors are uncommon lesions, usually found incidentally, which encompass roughly 2% of all musculoskeletal tumors.[3,4] They arise from the diploic space, internal and external tables of the calvaria, a subpart of the neurocranium, comprised of both parietal

bones, the interparietal part of the occipital bone, the squamous part of both temporal bones, and both frontal bones. The cranial vault is formed through the process of intramembranous ossification. At the same time, the second part of the neurocranium or skull base originates from the process of endochondral ossification – a fact worth considering when narrowing the differential diagnosis of skull lesions/tumors, alongside attenuation of the tumor, multiplicity, its extent, and patient's age. Skull tumors can be benign or malignant, primary or secondary, and lytic, and sclerotic or transdiploic (originating from intracranial, extra-axial soft-tissue and overcoming internal and/or external table) depending on their radiographic features, with metastasis being the most common skull tumor.[6,8] On the other hand, skull vault lymphomas (cranial vault lymphomas – CVLs) are exceedingly rare, especially primary lymphomas, and can pose a diagnostic challenge as they can resemble meningiomas.[2,5,7] Chronic lymphocytic leukemia/small cell lymphoma (CLL/SLL) is a mature B-cell neoplasm characterized by the accumulation of neoplastic small lymphocytes typically in the bone marrow, peripheral blood, lymph nodes, and other lymphoid organs such as spleen and liver. Other presentations are infrequent, especially as soft masses arise from the bone resembling multiple myeloma. Herein, we present a unique case of a systemic CLL/SLL infiltrating cranial vault as a "*helmet*" appearing lesion, with complete regeneration of destroyed skull bone after treatment with ibrutinib.

CASE DESCRIPTION

A 63-year-old female patient was admitted to our hospital in May 2019 for additional hematological work-up and treatment of CLL, which presented with lymphocytosis, discrete generalized lymphadenopathy, and osteolytic lesions of the Th10, Th11, and L2 vertebrae described on computed tomography (CT) scans of the thorax, abdomen, and pelvis in another hospital. Her general condition was poor due to hypercalcemia. Hypercalcemia was associated with normal phosphate serum levels and slightly elevated alkaline phosphatase but without any evident increase in parathyroid hormone serum levels, leading to the conclusion that hypercalcemia was not caused by disorders of the parathyroid glands but most probably a manifestation of a paraneoplastic syndrome in CLL with additional bone destruction. Soon after bisphosphonate administration, the calcium level normalized; however, she was still psychomotorically impaired. A head CT scan revealed diffuse destruction of the diploic space of the calvaria, alongside internal and external table destruction in certain places [Figure 1]. A fine needle aspiration was performed, and the finding was consistent with small lymphocyte infiltration in accordance with the bone marrow biopsy. Considering her poor condition due to progressive CLL/SLL, after initial corticosteroid therapy, a treatment with monoclonal anti-CD20 antibody (obinutuzumab) therapy was initiated. Her condition gradually improved, and she was treated in day hospital. However, after three cycles, her condition worsened again due to hypercalcemia despite once monthly treatment with pamidronate.

For that reason, she was hospitalized again during August and September of the same year and the control head CT scan showed progression of the destruction of the occipital, both parietal and a part of the frontal bone, where the external table was destroyed by a soft-tissue process that also partially permeated the internal table of the occipital and parietal bones on the right side, forming a sort of "*helmet*" like CVL [Figure 2]. The process was hyperdense, measuring 6 mm of width frontally and 13 mm parietally, and there were no signs of extra-axial and/or intra-axial collections/tumors. Brain (head) magnetic resonance imaging (MRI) was not performed as the patient was anxious and agitated due to confinement in the MRI.

This unusual presentation of CLL/SLL with bone tropism prompted us to exclude plasmacytic differentiation of CLL/SLL or Richter transformation to aggressive non-Hodgkin lymphoma (NHL). Bone marrow and lymph node biopsy were repeated, alongside fine-needle aspiration biopsy of the CVL confirming B-cell NHL, CLL immunophenotype, with a low proliferation index (Ki67 positive in 10% of cells). The findings of the fine-needle aspiration biopsy were not consistent with the patient's clinical picture, as a strong suspicion of an aggressive subclone with a high tropism toward bone existed. Therefore, a neurosurgical procedure was performed in general anesthesia in the form of a piece-meal biopsy of the tumor for histological diagnosis [Figure 3].

Histological diagnosis revealed a B-cell non-Hodgkin lymphoma, CLL immunophenotype, but with a higher proliferation rate than expected in indolent lymphoma (Ki67 positive in approximately 40% of cells), confirming an aggressive subclone [Figure 4]. Ibrutinib, an oral Bruton kinase inhibitor, was initiated with regular administration of bisphosphonate therapy. The patient's condition improved again.

The disease progressed again after 6 months of ibrutinib therapy (March 2020). Interestingly, the non-contrast head CT scan did not visualize the previously described bone destruction except a minimal patch high on the frontoparietal convexity of the skull [Figure 5], while the contrast-enhanced head CT scan showed no intra-axial or extra-axial pathological accumulation. The CT scan of the neck, thorax, abdomen, and pelvis showed further enlargement of all the

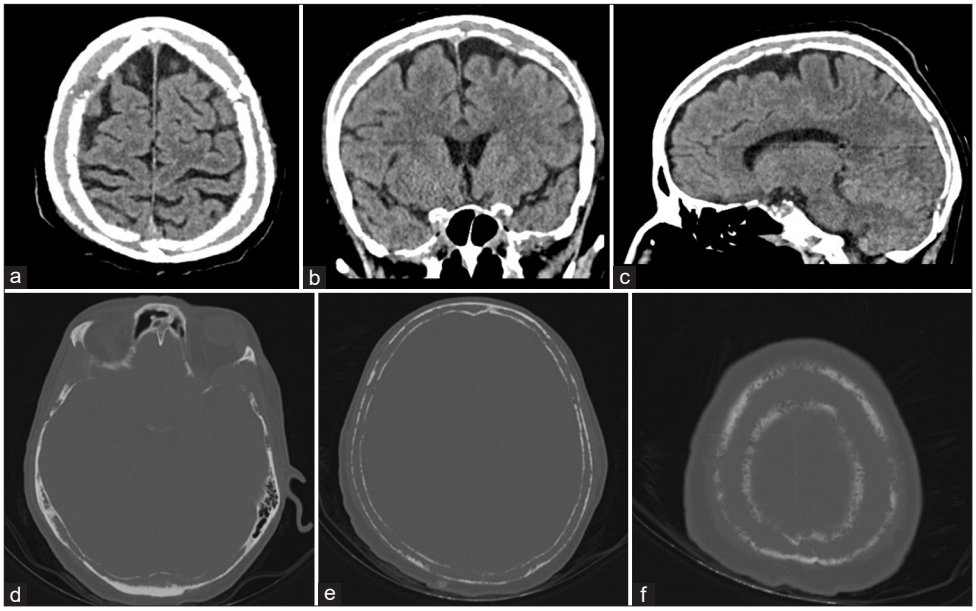

Figure 1: Non-contrast head computed tomography (CT) scan. (a) Axial slice showing the destruction of the diploic space (permeating growth pattern) of frontal and both parietal bones; (b) coronal slice, infiltration of the diploic space; (c) sagittal slice, the extent of tumor from the frontal to the occipital bone can be seen; and (d-f) CT scan bone window, axial slices at various levels showing diploic space destruction with mostly preserved internal and external table.

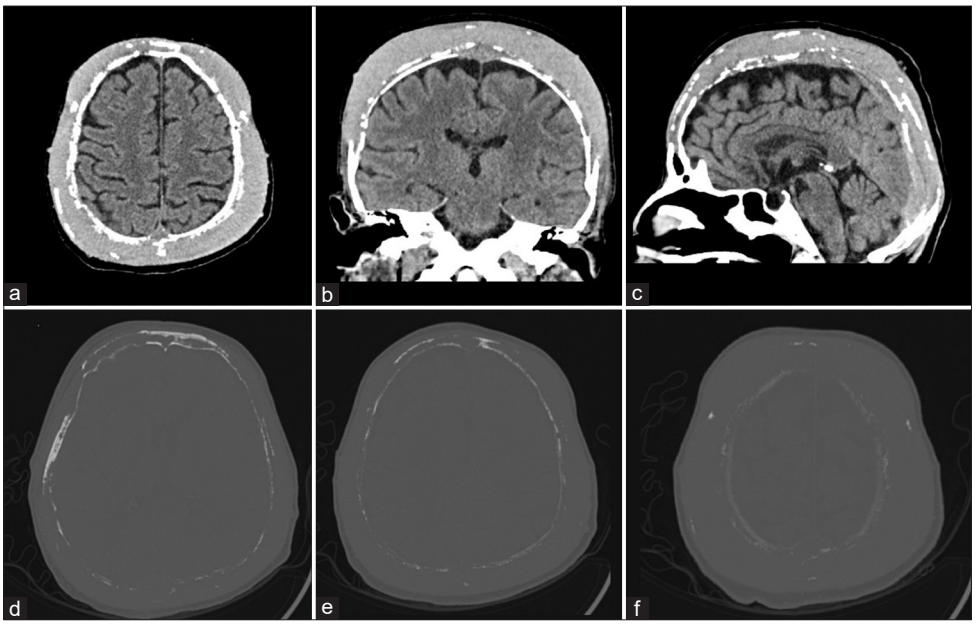

Figure 2: Non-contrast head computed tomography (CT) scan. (a) Axial slice, enlargement of the tumor with the effacement of the external table, the internal table is still somewhat preserved; (b and c) coronal slice and sagittal slice, respectively, showing a "helmet" form of the tumor; and (d-f) CT scan bone window, axial slices at various levels showing the destruction of the external table, with somewhat preserved internal table.

lymph nodes. Due to the progression of the disease, third-line therapy was initiated with venetoclax, a bcl-2 inhibitor, alongside pamidronate application.

The further course of the disease was complicated by pancytopenia requiring dose-reduction. Three months after venetoclax introduction, sternal bone marrow aspiration for

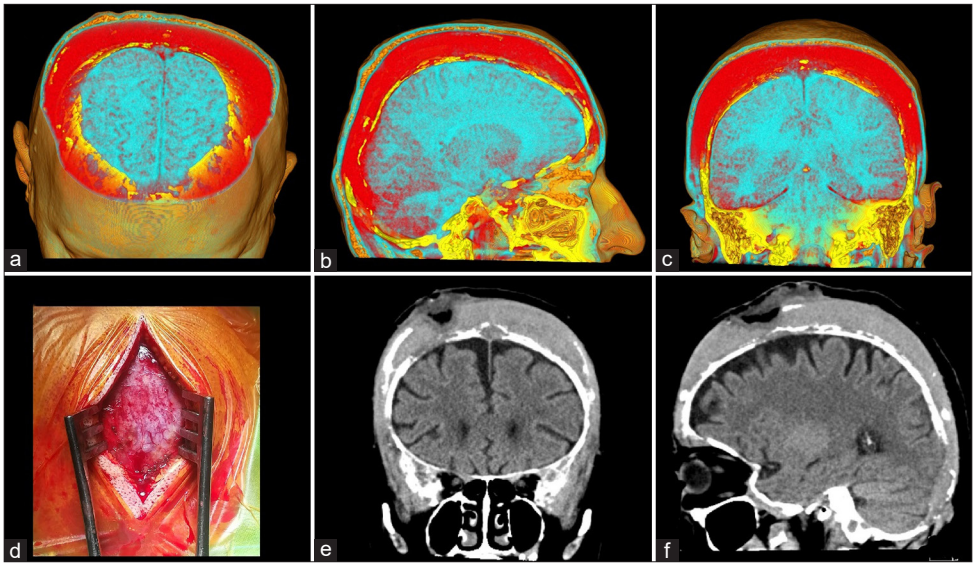

Figure 3: Neurosurgical procedure. (a-c) Axial, coronal, and sagittal slice reconstruction using OsiriX MD program showing the "helmet" CVL (red color); (d) intraoperative appearance of the tumor; and (e and f) non-contrast head computed tomography scan, coronal, and sagittal slice, respectively, showing the site of the operation at the level of the right Kocher's point.

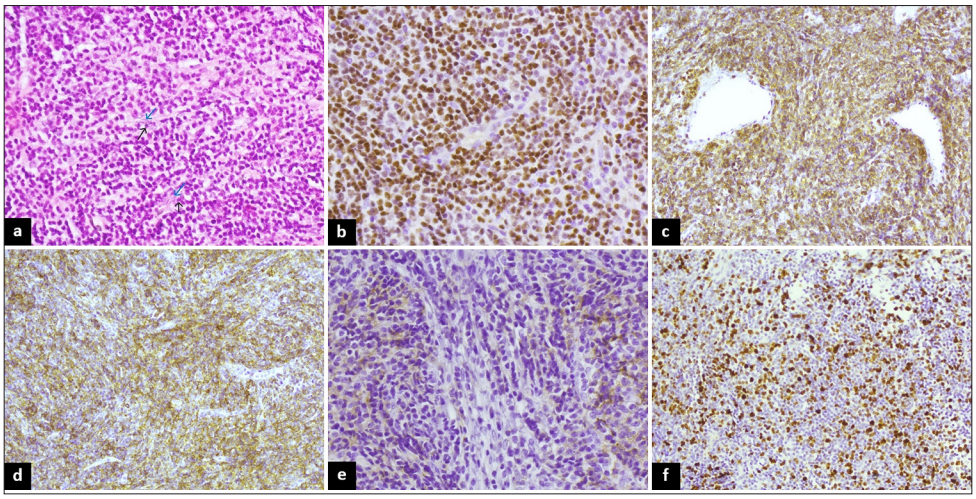

Figure 4: Histological biopsy findings. (a) Diffuse proliferation of small lymphocytes. Comparison of the size of the nucleus of a small lymphocyte (black arrow) to the nucleus of an endothelial cell (blue arrow), H&E staining, magnification ×400. The immunohistochemical analysis findings were consistent with CLL (b-d). (b) Pax5 nuclear positivity, magnification ×400; (c) CD5 membrane positivity, magnification ×200; (d) CD23 membrane positivity, magnification ×200; (e) CD20 weak membrane positivity due to previous therapy, magnification ×200; and (f) Ki67 nuclear positivity, magnification ×200.

the first time verified the presence of lambda clonal plasma cells along with CLL/SLL cells. The rising monoclonal spike in the serum protein electrophoresis was also observed. Therefore, bortezomib, a proteasome inhibitor routinely used for multiple myeloma, was added to venetoclax. Unfortunately, a month later, the patient died of a stroke. Interestingly, the last CT scan of the head revealed no tumor on the cranial vault.

DISCUSSION

CVL is a rare entity that can be divided into primary and secondary skull lymphomas. Solitary bone lesions are considered primary CVLs, while secondary CVLs are tumors originating from the surrounding tissues such as lymph nodes, organs, or soft tissue and secondarily invading

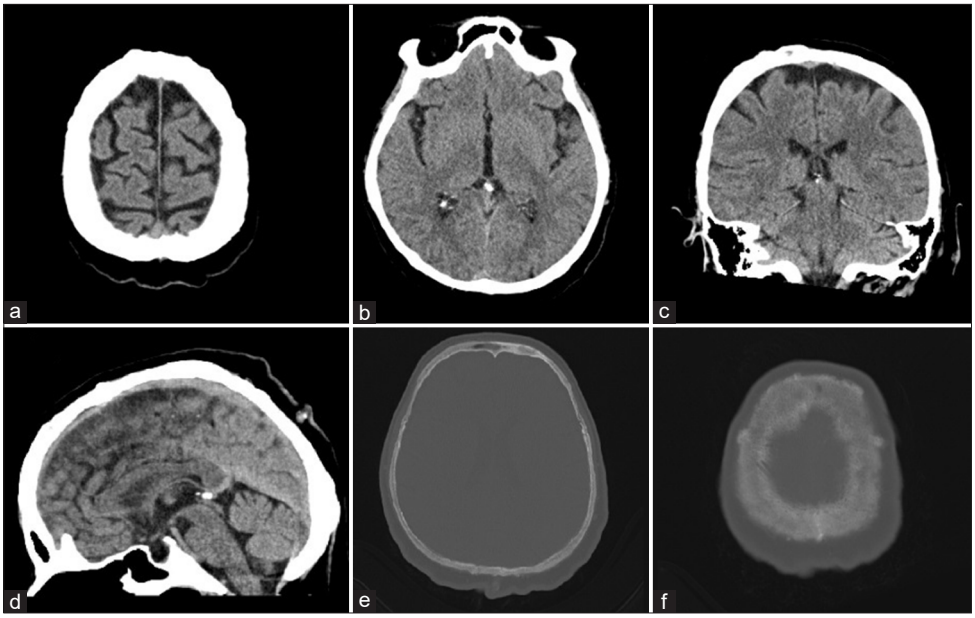

Figure 5: Non-contrast head computed tomography (CT) scan. (a and b) Axial slices at different levels showed no previous bone destruction, with clearly visible bone; (c and d) coronal and sagittal slices, respectively, showing no visible tumor; (e and f) CT scan bone window, axial slices at various levels showing well-formed bone with its diploic space, internal and external table.

skull bones.[2] A more rigorous definition of primary bone lymphoma requires the absence of disease at other sites and no evidence of systemic dissemination up to 6 months after the bone lymphoma detection.[10] Therefore, it is safe to presume that our case describes a secondary CVL due to evident systemic dissemination of the disease.

This case shows a unique presentation of a CVL extending through the whole calvarium, which contrasts the established opinion of a disproportionately small and mild skull destruction, preserved skull contours, and extensive soft-tissue mass observed by neuroradiological imaging (CT, MRI) in CVL patients.[2,7] CVLs usually have intra- and/or extracranial extension, while CVLs without extra- and/or intracranial extension are present in only 1% of cases. The most common type of skull change is an osteolytic lesion (81% of lymphomas), followed by those with preserved skull contour, hyperostosis, and finally, only sclerosis. Osteolytic lymphomas usually have a characteristic permeative dissolution (permeating growth pattern) with preserved skull contour or, to a lesser degree, a disolvement or penetration of less than half of the skull thickness.[5,7] While our case has a permeating growth pattern which is the most common type of presentation of osteolytic CVLs, there are no reports in the literature, to our understanding, with similar extensive destruction of the cranial vault. This case describes a rather striking and unique presentation of a CVL in the form of a helmet-shaped skull lesion with no intracranial or extracranial extension.

While most of the CVLs reported by Nitta *et al*. were diffuse large B-cell lymphomas (DLBCLs), there were only a few mentions of a SLL, which is interchangeably used with CLL.[7] CLL/SLL represents an indolent type of NHL, while DLBCL is an aggressive type of NHL. Da Rocha *et al*. reported a series of 5 CVL patients and conducted a systematic review of the literature regarding CVL, with 39.3% of CVL patients (28 patients from literature + their own 5 patients) having DLBCL, while only 5/33 patients (15,1%) had SLL.[5] A meta-analysis by Toyota *et al*. included 62 patients with NHL calvarial lesions, with the most common subtype being DLBCL (61% of all CVLs), followed by unspecified or mixed subtypes of B-cell lymphomas (18%), Burkitt lymphoma (5%), and small lymphocytic lymphoma (5%).[9] The current case' extensive CVL is caused by an aggressive subclone of the otherwise indolent type of CLL/SLL. This unique presentation is probably caused by unobstructed infiltration of the diploe spaces by highly aggressive lymphoma cells, with a pronounced tropism toward the skull bone.[2] Furthermore, no plasmacytic differentiation was observed from this case's repeated cranial vault tumor cell analysis.

Approximately two-thirds of reported primary CVLs were treated surgically, which was especially pronounced in the case of discrete lesions. However, in their meta-analysis,

Toyota *et al*. emphasize that a surgical procedure's role in CVLs is limited and often brings unnecessary risk, as a core needle biopsy, eventually followed by full-thickness scalp biopsy, suffice in acquiring a final diagnosis. This approach leads to remission at comparable rates, using chemotherapy and radiation while avoiding open surgery.[9] Although fine-needle aspiration biopsy with cytomorphology and flow cytometry may confirm secondary infiltration by CLL/SLL, this peculiar case required additional intervention in the form of an open, surgical biopsy as the diagnosis obtained through fine-needle aspiration did not coincide with the clinical and radiological presentation of the tumor. Indeed, a more aggressive subclone of CLL/SLL with a higher proliferation index was identified, yet without evidence of transformation to aggressive lymphoma or myeloma. Interestingly, plasmacytic transformation was eventually detected in the bone marrow as a new subclone emerging after subsequent venetoclax treatment.

Only two cases regarding bone regeneration of a previously affected cranial vault were reported in the literature. In both these cases, the main culprit was DLBCL with intracranial and extracranial involvement, which was successfully treated with chemotherapy with or without radiotherapy.[1,9] Due to poor general condition, our patient was treated primarily with obinutuzumab monotherapy that decreased the number of circulating CLL/SLL cells, however without any effect on the cranial vault component of the disease and the hypercalcemia (venetoclax and obinutuzumab combination was not approved for the first-line treatment at the time). In contrast, the cranial vault tumor completely regressed on ibrutinib; however, systemic progression was detected after only 6 months. This case presents a regeneration of a previously destroyed cranial vault after targeted agent treatment without the administration of radiotherapy. While the extensive osteolytic change was present inside the diploe in the form of a permeative growth pattern where the osteoclasts stimulated with cytokines and tumor cells directly resorbed bone matrix, the preserved dura and periosteum may have played a crucial role in bone regeneration.[1] The combination of ibrutinib (inhibitor of Bruton's tyrosine kinase) and pamidronate (bisphosphonate agent) therapy led to bone regeneration through clearing of NHL cells in the cranial vault and inhibition of osteoclast-mediated bone resorption, respectively.

Therefore, the current case shows not only a unique, extensive CVL with the destruction of the diploic space (permeating growth pattern) and effacement of the external table of the calvaria but also a dramatic bone regeneration after successful CVL treatment. On its own, it's not unusual for an osteolytic lymphoma to have a characteristic permeative dissolution, but such an extensive lesion forming a somewhat "*helmet*" form has not yet been documented. Another specificity of this case is that it was caused by the CLL/SLL, a type of NHL, which is usually indolent but, in this case, had an aggressive subclone with a significant tropism toward the skull bone.

CONCLUSION

Although most CVLs present as an extensive soft-tissue mass with disproportionately mild skull destruction, striking features like extensive permeative dissolution of the whole cranium vault can occur. This impressive neuroradiological finding may be seen even in usually presumed indolent types of lymphomas, like CLL/SLL. Regardless, even such large lesions can be successfully treated, given that adequate analysis is acquired beforehand. In the case of suspicion or inconsistencies between clinical presentation and core-needle biopsy or fine-needle aspiration findings, we believe that a surgical biopsy should suffice. Targeted therapy with Bruton kinase inhibitor in this type of CVL led to bone regeneration. Despite the well-known fact about the lack of potential for generalizing using case reports, we still emphasize the importance of publishing such peculiar cases to characterize unique tumor biology and clonal evolution during treatment with novel agents.

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