1 | INTRODUCTION

Richter transformation (RT) refers to the development of an aggressive B-cell lymphoma in patients with chronic lymphocytic leukemia (CLL).1,2 The incidence rate of RT among CLL patients ranges from 2% to 10%.3,4 Risk factors include advanced stage, lymph nodes larger than 3 cm, unmutated immunoglobulin heavy chain variable region gene (IGHV), presence of 17p deletion (del[17p]) and/or TP53 mutation, NOTCH1 mutation and stereotyped B-cell receptor (BCR).5,6

Histologically, RT presents as diffuse large B-cell lymphoma (DLBCL) in over 90% of cases and as classical Hodgkin lymphoma (HL) in up to 5% of cases.2,4 Regarding Hodgkin’s variant of RT (HL-RT), two histopathological categories have been described: type 1 is characterized by the presence of scattered Hodgkin and Reed–Sternberg (HRS) cells in a background of typical CLL; in type 2, the HRS cells are surrounded by an inflammatory milieu of T-lymphocytes, histiocytes, eosinophils and plasma cells.5,6 Epstein–Barr virus (EBV) can be frequently demonstrated in HRS cells (either by staining for latent membrane protein 1 [LMP1] on immunohistochemistry or by in situ hybridization of EBV-encoded RNA transcripts), and it has been postulated that RT might be triggered by EBV infection.7,8 While most cases of DLBCL variant of RT (DLBCL-RT) are clonally related to CLL, HL-RT is frequently unrelated to the CLL clone, with clonally related cases having a much worse prognosis.7,9,10 Data concerning HL-RT outcome are scarce; the available evidence shows that these patients have an inferior prognostic outcome than those with de novo HL, but superior survival compared to those with DLBCL-RT.1,6

Abstract
Hodgkin’s variant of Richter transformation is a rare complication of chronic lymphocytic leukemia and is associated with inferior outcomes compared to de novo Hodgkin lymphoma. Further data concerning prognosis and treatment of Hodgkin’s variant of Richter transformation occurring in the setting of novel targeted therapies are needed.

Keywords
chronic lymphocytic leukemia, Hodgkin lymphoma, ibrutinib, Richter transformation

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Novel, oral, targeted therapies, including the Bruton’s tyrosine kinase (BTK) inhibitor, ibritinib, and the B-cell lymphoma 2 (BCL2) inhibitor, venetoclax, have revolutionized the CLL treatment paradigm. Given their expanding role in CLL management, an increasing number of reports of RT occurring in this setting may be expected in the coming years.

2 | CASE REPORT

A 47-year-old female patient presented with a medical history of a right thigh atypical lipomatous tumor/well-differentiated liposarcoma diagnosed in 2009, treated with surgical resection and radiation therapy with a sustained complete remission.

In March 2018, a high lymphocyte count (12.5 × 10^9/L) was detected in routine blood analysis. Smudge cells were observed on the blood smear. Other parameters were normal, including hemoglobin (14 g/dl), platelet count (210 × 10^9/L) and lactate dehydrogenase (LDH; 189 U/L [normal range below 250 U/L]). Flow cytometry of peripheral blood showed that 40% of nucleated cells were B-lymphocytes expressing CD19, CD5, CD20 dim, CD23, CD43 and CD200 bright. The patient was asymptomatic, and clinical examination revealed no lymphadenopathy or splenomegaly. Therefore, a diagnosis of CLL Rai 0/ Binet A was established.

The patient was kept under watchful waiting until May 2020. At this time, she presented a lymphocyte doubling time of <6 months (with an absolute lymphocyte count of 53.2 × 10^9/L), as well as rapidly enlarging and symptomatic cervical and axillary lymph nodes (the largest measuring 3 cm in short axis). LDH was mildly elevated (lower than 2 times the upper limit of normal [ULN]), as well as beta-2 microglobulin (5.4 mg/L [normal range between 0.97 and 2.64 mg/L]); there was no anemia (hemoglobin level of 12 g/dl), and the platelet count was normal (211 × 10^9/L). B symptoms and organomegalies were absent. Interphase fluorescence in situ hybridization (FISH) was negative for del(17p13.1), but TP53 gene was mutated (c.574C>T [p.Gln192Ter], variant allele frequency 7%). Immunoglobulin heavy-chain variable region gene (IGHV) mutational status was unmutated, stereotyped subset #1 (IGHV1-18*01/IGHD3-22*01/IGHJ4*02). Treatment with ibritinib 420 mg id was started in June 2020, in addition to prophylactic acyclovir and trimethoprim/sulfamethoxazole. During the first 4 months of therapy, the patient did not experience any side effects and achieved a partial remission. She then began to experience daily high-grade fevers (up to 39°C, at time intervals of <8 h), accompanied occasionally by lower back pain and diarrhea. Physical examination was unremarkable. Blood tests showed a significantly elevated C-reactive protein (CRP) level (>20 mg/dl), LDH below 2 times ULN, a progressively worsening cholestatic pattern of liver function analysis (alkaline phosphatase and γ-glutamyl transpeptidase 2–3× ULN, with normal serum bilirubin), de novo microcytic anemia (hemoglobin level of 8–10 g/dl; mean corpuscular volume of 75–80 fl) and de novo normal to slightly elevated lymphocyte count (up to 10 × 10^9/L). A wide range of microbiological and serological tests were performed, and the patient was started on empirical antibiotic therapy. Given the absence of clinical improvement and the lack of a demonstrable infectious etiology, a thoraco-abdominopelvic computed tomography (CT) scan was performed and showed bilateral axillary lymphadenopathies (the largest one on the left axilla, measuring 28 × 15 mm); multiple abdominal lymphadenopathies (hepatic hilar, celiac, mesenteric, para-aortic and external iliac), the largest one measuring 34 × 26 mm; and mild hepatosplenomegaly. Additionally, 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET/CT) was performed. This scan revealed numerous supra and infradiaphragmatic enlarged hypermetabolic lymph nodes, with multiple abdominal conglomerate lymph node masses, the largest one below the left renal artery, with a longitudinal axis of 85 mm and maximum standardized uptake value (SUVmax) of 13.6; moderate hepatomegaly, without identifiable focal 18F-FDG–avid lesions; spleen in the limit of normal size, with increased 18F-FDG uptake (SUVmax 5.6); bilateral hypermetabolic adrenal nodules, the largest one with long axis 20 mm and SUVmax of 9.9; and diffuse homogeneous increased 18F-FDG uptake throughout the axial and proximal appendicular skeleton, suggestive of physiologic reactivity (Figure 1). These findings were suggestive of CLL transformation into a hypermetabolic tumor. A CT-guided core needle biopsy of the abdominal nodal mass with the highest 18F-FDG uptake was performed. Histopathological analysis showed a lymphoproliferative neoplasm composed of small monomorphic lymphocytes with scant cytoplasm and hyperchromatic nuclei, positive for CD45, CD19 and CD5 and focally for CD20 and CD23, cytoplasm and nuclei with irregular contour and prominent nucleoli, occasionally binucleated, resembling HRS cells; immunohistochemistry study showed positivity of these cells for CD30, CD15, MUM1 and PAX5, the latter with weak intensity; these findings were consistent with a diagnosis of type 1 Hodgkin’s variant of RT (Figure 2).

Tumor cells were negative for EBV encoded RNA (EBER). A diagnosis of HL-RT, Ann Arbor stage IV-B, International Prognostic Score (IPS) 4, was established. Ibrutinib was discontinued, and the patient started treatment with adriamycin, bleomycin, vinblastine and dacarbazine (ABVD). After
A single cycle of chemotherapy, a clinically significant improvement was already noticeable, with resolution of fever and constitutional symptoms. Simultaneously, there was a progressive improvement of blood counts, liver enzymes and CRP. The interim PET/CT scan performed after two cycles of ABVD showed a complete metabolic response (Deauville score 2), and the patient proceeded to four additional cycles of chemotherapy with omission of bleomycin (i.e., AVD), as per protocol. She completed chemotherapy without any major adverse events. End-of-treatment PET/CT

**FIGURE 1** Numerous supra- and infradiaphragmatic enlarged hypermetabolic lymph nodes, splenic and adrenal hypermetabolic involvement, suggesting high-grade transformation of CLL. 3D whole body (A), PET (B), CT (C) and PET/CT (D) coronal images

**FIGURE 2** Histopathological examination showed large pleomorphic neoplastic cells scattered on a background of small monomorphic lymphocytes (H&E stain, 200× magnification) (A). Small lymphocytes were positive for CD5 (B); this and other immunohistochemical features were consistent with CLL. Large pleomorphic neoplastic cells were positive for CD30 (C) and CD15 (D); these cells had characteristic morphological and immunohistochemical features of HRS cells.
(performed 6 weeks after the last cycle) was consistent with a complete metabolic response (Deauville score 1). Despite ibrutinib being discontinued after the diagnosis of RT, complete hematologic response has been maintained thus far; peripheral blood flow cytometry performed 2 months after the last cycle of AVD and approximately 10 months after ibrutinib withdrawal identified 0.45% of clonal B cells with a CLL phenotype.

At the time of writing, the patient is being closely monitored for relapse of both CLL and HL-RT as well as for late treatment toxicities.

3 | DISCUSSION

Diagnosis of RT often requires a high index of suspicion, given the relatively nonspecific signs and symptoms, which include high-grade fevers, rapidly enlarging lymph nodes, weight loss, hypercalcemia and/or a markedly elevated LDH. In this case, the diagnosis of HL-RT was difficult, reflecting its rarity and the overlap of its signs and symptoms with several medical conditions (including infectious, malignant and rheumatic/inflammatory diseases).

Our patient was diagnosed with RT 4 months after ibrutinib initiation. This is in line with published data, suggesting that progression with RT on ibrutinib therapy tends to occur early on treatment. Several studies suggested that EBV may have a role in B-cell transformation and induction of resistance to apoptosis, which may lead to CLL progression. Indeed, many cases (67%–76%) of HL-RT show EBV positivity. In the case described above, however, HRS cells were EBER-negative.

Due to its high sensitivity and negative predictive value, 18F-FDG PET scan has a role in the diagnosis of RT. Several studies suggested that a SUVmax greater than or equal to 5 on PET/CT is a reliable cutoff to identify CLL patients with clinically suspected RT. Additionally, 18F-PET/CT may be useful to select the optimal site for performing a diagnostic biopsy. Wherever possible, excisional biopsy is always preferred. In our patient, however, the sites of FDG-avid disease were not easily accessible for an excisional biopsy. A CT-guided percutaneous core needle biopsy of FDG-avid abdominal conglomerate nodal mass was therefore performed and played a critical role in establishing an accurate diagnosis.

Regarding prognostic stratification, the IPS, originally developed for de novo HL, may be used for patients with HL-RT, with an IPS greater than or equal to 4 being significantly associated with a lower likelihood of obtaining a CR.

The optimal chemotherapeutic approach for HL-RT remains to be established. ABVD is the most used regimen, with a complete response (CR) rate of 68% in one retrospective study. Although ABVD seems to be an effective therapeutic strategy, a number of patients eventually develop relapsed disease after a short period of time. Indeed, in a retrospective study including 18 patients with HL-RT, the median failure-free survival duration was only 0.4 years, suggesting that more effective treatments are needed for patients who have HL-RT.

While hematopoietic stem-cell transplantation (SCT) is a well-established indication as postremission consolidation therapy for transplant-eligible patients with DLBCL-RT (especially for those with clonally related disease), the role of SCT, either autologous or allogeneic, is not well-defined in HL-RT. Given the lack of data for SCT in HL-RT patients who achieve a CR after first-line therapy, these are typically observed until progression, with SCT being reserved for those eligible patients with relapsed/refractory disease.

In patients exposed to targeted CLL therapies (including BTK and BCL-2 inhibitors) or prior chemoimmunotherapies, the management of RT may benefit from the usage of novel agents (for example, checkpoint inhibitors), which have shown promising results in multiple studies. However, further data on the role of molecular-targeted therapies are needed.

4 | CONCLUSION

We herein report a rare case of HL-RT occurring during ibrutinib therapy, with successful attainment of a complete remission following treatment with ABVD/AVD regimen. The case illustrates the difficulty in establishing this diagnosis and the importance of considering HL-RT in the differential diagnosis of CLL patients presenting with constitutional symptoms. Given that remission duration after ABVD therapy is often short, further studies on newer, intensified treatment approaches are required, as well as on the role of high-dose chemotherapy and autologous/allogeneic stem-cell transplant as a consolidation strategy.

AUTHOR CONTRIBUTIONS
CA, MG, MIP, CG and JPC were involved in patient care and contributed to the manuscript preparation. CF and RF are pathologists who contributed to the patient’s diagnosis. TS is a nuclear medicine radiologist who analyzed the PET/CT scan performed at the time of diagnosis.
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CONFLICT OF INTEREST
CA - Invited speaker for Janssen. MG - Participation in advisory boards from Takeda, Janssen, Abbvie, Roche. Invited speaker for Janssen, Takeda, Gilead Sciences, Roche. Consultancy and teaching for Janssen and Takeda. CG - Consultancy, scientific lectures and participation in advisory boards from Celgene/BMS, Janssen, Amgen, Takeda, Sanofi and Gilead. JPC - Consultancy and participation in advisory boards from Janssen, Gilead Sciences, BMS, Abbvie, Takeda and Sanofi. Travel support from Roche, Janssen, Gilead Sciences, Abbvie. Consultancy and teaching for Janssen. MIP, CF, RP and TS - No conflicts of interest to report.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article, and data used to support this study are included within the article.

ETHICAL APPROVAL
Ethical approval for publication was obtained.

CONSENT
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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