Hairy cell leukemia with isolated bone lesions

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Abstract

Bone lesions are rarely reported in Hairy Cell Leukemia (HCL). We report two BRAFV600E mutated HCL patients presented bone lesions at foreground, poor bone marrow involvement and the important role 18F-FDG PET/CT played in their management. We discuss the crucial role that 18F-FDG PET/CT could play in HCL routine practice.

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Running title: Hairy cell leukemia and bone lesions

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Key Clinical Message:

18F-FDG PET/CT has clinical relevance in HCL at diagnosis and for the follow-up of patients treated, especially in case of atypical presentations such as bone involvements (which are probably underestimated) and poor bone marrow infiltration.

Keywords : Hairy cell leukemia, HCL, Bone lesions, 18F-FDG PET/CT, PNA, Cladribine, Rituximab

Consent

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy

Highlights

What is the new aspect of your work? Hairy cell leukemia (HCL) is a rare disease and bone lesions are very unusual at diagnosis. We describe two typical HCL patients, who present at diagnosis bone lesions: right frontal tumefaction above the eyebrow and right femoral localization, respectively. In both cases, the bone marrow infiltration was moderate and the bone biopsies showed a typical infiltration with hairy cells.

What is the central finding of your work? ^{18}F-FDG PET/CT could be a useful tool for the HCL diagnosis by guiding the bone biopsy and for the follow-up of the patients treated by cladribine (CDA) and rituximab (R).

What is (or could be) the specific clinical relevance of your work? The detection of bone lesions is crucial in HCL and could require^{18}F-FDG PET/CT. The bone marrow infiltration by hairy cells could be moderate, requiring bone biopsies. The association CDA plus R could be very effective, allowing a complete remission (CR) in both cases with a durable CR in one case reaching more than 8 years.

1. Introduction

Typical clinical features of hairy cell leukemia (HCL) are cytopenias related to bone marrow infiltration and splenomegaly. Skeletal localization is a rare but well-recognized complication, mostly identified by painful osteolytic lesions in the proximal portions of long bones, although bone presentations with exclusive bone pain and few clinical and biological symptoms at presentation have been reported (1). Unusual presentation may pose a significant diagnosis challenge in routine practice. Only a few cases of HCL patients who have had a^{18}F-FDG PET/CT have been published but all of them showed hypermetabolic localizations (1). Here, we report two cases of patients treated at the same medical center eight years apart from each other, with singular presentation of HCL characterized by threatening bone damage and lack or moderate bone marrow infiltration, and for whom^{18}F-FDG PET/CT had an important role. The therapeutic options combining cladribine (CDA) and rituximab (R) were very effective, allowing durable complete remission (CR).

2. First case

The first case was a 59-year-old woman in 2012 with no past history, who presented with a painful right frontal tumefaction above the eyebrow. No growth bone or other abnormality was observed at the radiography. The scan showed a frontal anterior right tissue process up to the external part of the right frontal sinus and a lytic bone lesion beginning at the right orbit roof. The biopsy of the frontal lesion was inconclusive and suggested only a chronic lymphoproliferative disorder (CLPD) without further clarification. Proofreading of the frontal bone biopsy confirmed a bone localization of HCL with a $BRAF^{V600E}$ mutation positive (mutation identified in 70-100% of typical HCL cases) (2). The bone marrow biopsy revealed moderate infiltration by hairy cells expressing DBA44, cycline D1 and CD20 as well. The markers of T-lymphoproliferation disorders and extramedullary plasmocytoma were negative. The bone marrow aspirate showed a smear of medium richness on which the different myeloid cell lines were correctly represented without morphological abnormalities. No excess of blasts was observed, despite the presence of medium-sized lymphoid cells with basophil cytoplasm, and often with "shredded" appearance and circular and reniform nucleus with the chromatin unpacked. This confirmed the presence of around 6% of lymphoid cells whose cytological appearance suggested hairy cells. The phenotype was compatible to hairy cells CD19+ monotypic kappa of moderate intensity CD5- CD10- CD20+ high CD22+ high CD79b+ CD23- FMC7- CD38+ CD43- CD44+ IgG- IgM+ IgD- CD11c+ CD25+ CD103+ CD123+. The immunological score of HCL was 4/4, excluding a variant presentation. In order to assess the extension consecutive to the histology of the frontal bone lesion, ^{18}F-FDG PET/CT was carried out. Three bone hypermetabolisms were reported: the known frontal bone lesion, one on the right semi-sacrum and the third on the hipbone, near the sacroiliac joint. The body scan did not identify focal lesion or lytic bone lesion at the hipbone but rather a bone densification, and no tumor syndrome was described. The patient was symptomatic only on the frontal lesion. The complete blood count was normal except for minimal thrombocytopenia: white blood cells at $4.8x10^9$/L composed of $3.07x10^9$neutrophils/L, $1.58x10^9$ lymphocytes/L and $0.1x10^9$ monocytes/L, hemoglobin was 14,2g/dL and platelets were at $148x10^9$/L (lower limit at $150x10^9$/L).

Because of long initial diagnostic wandering and the emergency of a treatment required in fear of a rapid progression of the orbit roof osteolytic lesion in case of diffuse large cell lymphoma, two cycles of CEP (cyclophosphamide, etoposide, prednisolone) were administered with no clinical benefit observed. As soon as the final histology of the bone marrow biopsy was received, the standard first-line treatment by purine analog, cladribine (CDA), was initiated.

Two months after the treatment, neither symptom nor pain, was reported by the patient. A complete response (CR) was obtained on both medical examination, blood count and scan. Six months after the treatment, the^{18}F-FDG PET/CT done described a disappearance of hypermetabolisms on the right frontal bone, and of the sacrum and right hip bone at pelvic girdle. However, the bone marrow aspirate evaluation done at the 6-month treatment evaluation showed normal bone marrow cytology without lymphoid cells but also minimal residual disease of hairy cells of 0.3% of bone marrow cells. A total of four weekly rituximab was subsequently administered. With a follow-up of eight years after the treatment, no objective relapse had occurred.

3. Second case

The second case was a 45-year-old man with no significant medical history presenting for several months with an increasingly painful right hip with functional limitations. No traumatism, barotraumastism, micro-traumatism or corticosteroid treatment was reported. Both pelvis and hip radiographs taken four months apart were normal. Bone scintigraphy revealed incomplete and non-displaced broken neck of the left thigh-bone. The right hip scan confirmed the results of the scintigraphy with osteolytic lesions of the lower part of the femoral neck and of the great trochanter and no bone callus or fracture displacement. In this context of pathologic bone lesions,^{18}F-FDG PET/CT was performed showing multiple hypermetabolic bone lesions (cervical thoracic spine, humeral heads, pelvis, femurs and left internal tibial fracture) but no organ was appreciably involved (Figure 1).

The bone biopsy of the right femur suggested a bone localization of HCL with BRAF mutation negative by FISH but pV600E/K/R exon 15 positive in molecular search (qqPCR), CD20 Annexin-A1 and DB44 were also positive, as shown in Figure 2. Hematologic malignancy was not expected, taking into account the normal complete blood count: white blood cell count was $6.1x10^9$/L composed of $3.46x10^9$neutrophils/L, $1.99x10^9$ lymphocytes/L, $0{,}58x10^9$ monocytes/L and no malignancy cells, hemoglobin 15,1g/dL and platelets $202x10^9$/L. Moreover, biochemistry and protein electrophoresis were strictly normal and there was no splenomegaly or lymphadenopathy at medical examination. More surprisingly, the bone marrow biopsy was within normal morphological limits without tumor cell infiltration. The bone marrow cytology in the center in charge of the patient found normal cytology with a smear of medium richness on which the different myeloid cell lines were correctly represented without any morphological abnormalities, no excess of blasts or abnormal lymphoid cells, plasma cells involvement was low and consisted in rare plasma cells with any dystrophy. A bone marrow sample was sent to a French expert center which, using multicolor multiparameter flow cytometry, showed $4{,}7x10^{-4}$kappa-restricted monotypic B cells of small-sized cells with CD11c, CD103, CD123 and CD25 expression (immunologic score: 4/4). Given the poor infiltration of the bone marrow, Nest Generation Sequencing (NGS) could not be performed. Flow cytometry was negative in the peripheral blood.

Although usual criteria of treatment were not met, a treatment was indicated because of the bone fracture. The patient received first-line therapy of HCL with purine analog, cladribine 0,14mg/kg J1 to J5 in subcutaneous to which monoclonal antibody anti-CD20, rituximab was added once a week during eight weeks. No surgical or radiotherapy indication was given. No side effects were observed. The response to treatment has been favorable with resolution of bone pain. On the blood count, only lymphopenia at $0{,}58x10^9$/L was observed due to the treatment, the rest was normal: white blood cells at $4.7x10^9$/L in which $3.32x10^9$neutrophils/L and $0{,}42x10^9$ monocytes/L, hemoglobin at 16g/dL and platelet count at $235x10^9$/L. The evaluation performed two months after treatment initiation was suggested a complete response. The ^{18}F-FDG PET/CT objectified absence of tumor infiltration and non-significant residual hypermetabolic fixations (humeral heads and left tibia), Figure 1. The bone marrow aspirate was normal in cytology with undetectable minimal residual disease. The bone marrow biopsy was normal and confirmed the CR.

4. Discussion

HCL is a rare indolent B-CLPD and represents 2% of all leukemias (2). Typical clinical features of HCL concern patients with a median age at diagnosis of 54 years with cytopenia (60-80%) and splenomegaly (80-90%) (3). However, HCL can have rare articulation, skin, hepatic, auto-immune or bone involvements (4-8). HCL was first described in 1958 by Bouroncle *et al* , and the first reported bone involvement (osteolytic type) occurred almost 20 years later, in 1977 by Rhyner*et al (9,10)*. Recently, a literature review of the MEDLINE database looking for articles relating only to bone lesions in HCL was performed by Robak *et al (1)*. Bone involvement was observed in about 3% (0-13%) of patients and very rarely observed at presentation. Thirty-six cases were reported: one-third had symptomatic bone lesions at the time of diagnosis, but the majority of bone involvement was demonstrated later, up to several years (from two months to 22 years). After review of the literature including known cases of HCL with skeletal involvement, clinical features could be more specified. Indeed, the data of Robak *et al* confirm the preponderant involvement of the femur (head, neck or both) estimated at 75% of the bone lesions in HCL (1). The second main localization of bone involvement is distributed in the axial skeleton (6). There are only a few similar case reports in the literature (6). Bone damage was mainly represented by osteolytic lesions but rare cases of severe osteoporosis and aseptic necrosis have also been described (1). Osteolytic lesions are nonspecific on imaging and the first etiologies considered are solid tumor metastases or myeloma, but the clinician must be vigilant about other diagnoses.

However, isolated bone presentation has been observed in HCL, with bone lesions strongly associated with high tumor burden and bone marrow infiltration (11). The main peculiarity of our two cases consisted in a very symptomatic clinical presentation with exclusive bone pain of increasing intensity that contrasted with a poorly informative biological workup (absence of cytopenia) in relation to a mild marrow infiltration. However, persistent bone pain of increasing intensity can be considered as typical of skeletal involvement in HCL, estimated at 89% of patients (1).

Although our case is an uncommon clinical disease presentation, the phenotype of hairy cell leukemia was typical with an immunological HCL score of 4/4 (12). Moreover, the $BRAF^{V600E}$ mutation was positive, excluding an HCL variant disorder (13). To note, a case mimicking multiple myeloma has also been reported in a patient presenting a painful upper left thigh with several hypermetabolisms at ^{18}F-FDG PET/CT and hypergammaglobulinemia with positive immunofixation for monoclonal immunoglobulin A. Neither hairy cells nor $BRAF^{V600E}$ mutation was identified in blood, bone marrow aspirate and bone marrow trephine biopsy from the iliac crest. The diagnosis of HCL was on the core biopsy of the left femoral neck showing hairy cells with the positive $BRAF^{V600E}$mutation (14). All these unusual clinical presentations exposed here should induce hematologists not to neglect HCL in diagnostic hypothesis in case of bone lesions and, above all, to carry out biopsy.

Concerning ^{18}F-FDG PET/CT, its place in care of HCL patients remains unclear and needs to be determined. Its use in HCL is quite recent and is still being developed. First of all, radiography is insufficient, many cases including ours had normal x-ray. Most of the time, a CT scan or MRI is performed as a second step and then sometimes a ^{18}F-FDG PET/CT. Only a few cases of patients with HCL who underwent ^{18}F-FDG PET/CT have been published and all of them showed hypermetabolic localization whether classical or not (5, 6, 15-17). Some studies indicate that ^{18}F-FDG PET/CT is an interesting tool for the evaluation of the extension of HCL. Indeed, all ^{18}F-FDG PET/CT of HCL patients with bone involvement show hypermetabolisms not only in areas of pain but also in areas without clinical translation, suggesting other existing or early asymptomatic bone lesions. MRI, while often used, is a less specific and less sensitive technology than ^{18}F-FDG PET/CT to detect multiple and/or early localizations. In light of these observations, it can be assumed that bone lesions at the time of diagnosis of HCL are underestimated since imaging is only performed in case of pain and not systematically at the time of discovery of the hemopathy. The delay between the appearance of a bone lesion related to HCL and the development of symptoms is therefore completely unknown. Other studies indicate that ^{18}F-FDG PET/CT is of interest in the evaluation of response to treatment (18). In HCL patients, ^{18}F-FDG PET/CT showed normalization of FDG uptake at all previously pathological sites following cladribine treatment (17). However, it is unclear whether ^{18}F-FDG PET/CT is sufficiently sensitive to determine residual disease, which is currently evaluated in bone marrow and blood (19). Based on these observations and our cases, we think that ^{18}F-FDG PET/CT seems to be quite reliable to assess the disease. An observational trial could be led first for epidemiological purposes in order to better characterize disease presentation, especially at diagnosis by the systematic ^{18}F-FDG PET/CT to better specify the frequency of bone involvement in HCL. All reported cases of HCL with bone involvement have been treated because of pain and not because of cytopenia or splenomegaly. However, Do asymptomatic non-threatening bone lesions found by routine ^{18}F-FDG PET/CT at diagnosis represent treatment criteria on their own? Due to low reported incidence, there exists no established recommendation for this group of patients with HCL with bone involvement. It is clear that this particular presentation needs to be better clarified as to its actual frequency, pathophysiology, prognosis, and response to treatment. Routine ^{18}F-FDG PET/CT would seem to be a first step to answering these questions. Moreover, this examination can guide a possible biopsy if necessary (notably to eliminate a differential diagnosis).

A quarter of patients with HCL are asymptomatic at diagnosis and require regular monitoring for a variable period of months to years before meeting at least one of the validated treatment criteria. These criteria are: absolute neutrophil count $<1x10^9$/L, hemoglobin <11g/dL, platelet count $<100x10^9$/L, symptomatic splenomegaly, infections or bleeding related to cytopenias (2). Purine nucleoside analogues (PA) (pentostatin and cladribine) remain the standard first-line treatment for HCL, achieving overall response (OR) rates of 90-100% and complete response (CR) in 70 to 90%. No significant difference between the two agents has ever been observed even if no randomized trials have compared both drugs (2,20). Remissions are durable (median 15 years), and survival is close to that for an age-matched general population (21,22).

Rituximab alone has not been formally tested in first-line therapy, but given the relatively low response rates seen in relapsed HCL, it is not recommended except in special circumstances: its use could be reserved for patients ineligible for purine analogues or who have an active infection. In contrast, it has been shown to improve remissions with a combination of rituximab and a PA (23,24). A recent publication comparing

concurrent rituximab with delayed rituximab ([?]6 months if minimal residual disease (MRD) is detected in blood) showed a marked improvement in MRD negative complete remission rates by concurrent rituximab. The CR rate was 100% with concurrent immunochemotherapy versus 88% with delayed administration, and the rates of undetectable MRD were 97% versus 24%, respectively. Immediate hematologic toxicity was greater (including transient grade 3-4 thrombocytopenia) but recovery was faster at 4 weeks compared with delayed rituximab (25). Chemoimmunotherapy combining cladribine (CDA) daily for five days and rituximab weekly for eight weeks (CDAR regimen) could be an alternative in high-risk HCL: splenomegaly $>$ 3cm, leukocytosis $>$ 1x10^9/L, hairy cells in the blood at 5x10^9/L, beta-2 microglobulin $>$ 2N, resistance to PNA, HCL CD38 positive or IGHV unmutated (2). However, neither treatment criteria nor risk stratification take into account unusual clinical presentations, including bone involvement, which is one of the most reported atypical presentations. Our first reported case (the female patient with the threatening right frontal tumefaction) was treated in 2012. At that time, rituximab just began to be used in HCL and data on its efficacy and safety were not yet available. According to the recommendations of the time, she received a CDA in monotherapy and rituximab was delayed because of the detection of MRD in bone marrow six months after PA administration. With therapeutic sequence, she achieved an excellent and durable response. She is still currently in remission. For the second case, we considered our young man's femur fracture as a high-risk criteria and opted for the CDAR association in light of recent studies in order to maximize the therapeutic response and eradicate the disease as long as possible in fear of a severe bone relapse even if, to date, we have no precise data on the response to the treatment and the prognosis of HCL with bone localizations compared to those with classical presentation. Radiotherapy was not applied for even if it is known that moderate doses are effective in supportive care, nevertheless, side effects are far from negligible and it is not a curative treatment of the disease.

5. Conclusion

These cases emphasize the importance of multimodality approaches, highlights the role of the ^{18}F-FDG PET/CT to detect rare or unusual HCL involvement and to drive biopsy. Although only small series of patients have been reported in the literature, atypical presentation in HCL is not uncommon and represents a significant diagnostic challenge in routine practice. ^{18}F-FDG PET/CT should become more prominent in the future at the time of diagnosis and in monitoring response in cases of unusual or atypical presentation. However, the pathological mechanism of this bone involvement with such low bone marrow involvement remains unclear.

Authors Contributions

LC, CG and CT participated in care of the patient and wrote the manuscript; SG, TS, AL, HG, FBM: participated in care of the patients and revised the manuscript content; EM, SB, CB, ED, JCC, AR and XT performed histological analysis and revised the manuscript content. All the authors reviewed and approved the final version of the manuscript.

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Conflict of Interest Statement

The authors declare no relevant conflict of interest.

Abstract (50 words)

Bone lesions are rarely reported in Hairy Cell Leukemia (HCL). We report two BRAF^{V600E} mutated HCL patients presented bone lesions at foreground, poor bone marrow involvement and the important role 18F-FDG PET/CT played in their management. We discuss the crucial role that 18F-FDG PET/CT could play in HCL routine practice.

References

Robak P, Jesionek-Kupnicka D, Kupnicki P, Polliack A, Robak T. 2020. Bone lesions in hairy cell leukemia: diagnosis and treatment. *Eur J Haematol* ; 105(6): 682-691

Maitre E, Cornet E, Troussard X. 2019. Hairy cell leukemia: 2020 update on diagnosis, risk stratification, and treatment. *Am J Hematol* ; 94: 1413-1422

Parry-Jones N, Joshi A, Forconi F, Dearden C, BSH guidelines committee. 2020. Guidelines for diagnosis and management of hairy cell leukemia (HCL) and hairy cell variant (HCL-V). *Br J Haematol* ; 191(5): 730-737

Tadmor T, Polliack A. 2015. Hairy cell leukemia: uncommon clinical features, unusual sites of involvement and some rare associations.*Best Pract Res Clin Haematol* ; 28(4): 193-199

Pattnaik SA, Padhi S, Chhabra G, Panigrahi MK, Das PK, Bhola RK, Mishra S. 2020. Atypical presentation of hairy cell leukemia: a report and comprehensive review. *Blood Res* ; 55 (2): 123-127

Yonal-Hindilerden I, Hindilerden F, Bulut-Dereli S, Yıldız E, Dogan IO, Nalcaci M. 2015. Hairy cell leukemia presenting with isolated skeletal involvement successfully treated by radiation therapy and cladribine: a case report and review of the literature. *Case Rep Hematol* ; 2015: 803-921

Rosen DS, Smith S, Gurbuxani S, Yamini B. 2008. Extranodal hairy cell leukemia presenting in the lumbar spine. *J Neurosurg Spine* ; 9(4): 374-376

Polliak A. 2002. Hairy cell leukemia: biology, clinical diagnosis, unusual manifestations and associated disorders. *Rev Clin Expo Hematol* ; 6(4): 366-388

Bouroncle BA, Wiseman BK, Doan CA. 1958. Leukemic reticuloendotheliosis.*Blood* ; 13:609-630

Rhyner K, Streuli R, Kistler GS. 1977. Hairy-cell leukemia with osteolytic bone changes. *Schweizerische Medizinische Wochenschrift* ; 107(25): 863-871

Lembersky BC, Ratain MJ, Golomb HM. 1988. Skeletal complications in hairy cell leukemia: diagnosis and therapy. *J Clin Oncol* ; 6(8): 1280-1284

Matutes E, Catovsky D. 1994. The value of scoring systems for the diagnosis of biphenotypic leukemia and mature B-cell disorders.*Leuk Lymphoma* ; 13 Suppl 1: 11-14

Tiacci E, Trifonov V, Schiavoni G, Holmes A, Kern W, Martelli MP, Pucciarini A, Bigerna B, Pacini R, Wells VA, Sportoletti P, Pettirossi V, Mannucci R, Elliott O, Liso A, Ambrosetti A, Pulsoni A, Forconi F, Trentin L, Semenzato G, Inghirami G, Capponi M, Di Raimondo F, Patti C, Arcaini L, Musto P, Pileri S, Haferlach C, Schnittger S, Pizzolo G, Foà R, Farinelli L, Haferlach T, Pasqualucci L, Rabadan R, Falini B. 2011. BRAF mutations in hairy-cell leukemia. *N Engl J Med* ; 364 (24): 2305-2315.

Notarfranchi L, Russo F, Re F, Mancini C, Martella E, Falini B, Aversa F, Tiacci E. 2019. Hairy cell leukemia mimicking multiple myeloma. Lancet Oncology; e187

Doma A, Skerget M, Zagar I. 2019. 18F-FDG PET/CT for staging and evaluation of therapy in a patient with unusual hairy cell leukemia presentation. *Clin Nucl Med* ; 44(7): e458-e460.

Wang L, Tadros AS, Hoh CK, Wang HY. 2016. CD-10 positive hairy cell leukemia involving multiple deep lymph nodes. *Clin Lymphoma Myeloma Leuk* ; 16(5): e51-53

Robak P, Jesionek-Kupnicka D, Kupnicki P, Polliack A, Robak T. 2021. Multifocal osteolytic lesions in hairy cell leukemia - the importance of PET/CT in diagnosis and assessment. *Ann Hematol* ; 100(6): 1641-1645.

Spedini P, Tajana M, Bergonzi C. 2000. Unusual presentation of hairy cell leukemia. *Haematologica* ; 85(5): 548

Filippi AR, Franco P, Marinone C, Tarella C, Ricardi U. 2007. Treatment options in skeletal localizations of hairy cell leukemia: a systematic review on the role of radiation therapy. *Am J Hematol* ; 82(11): 1017-1021

Grever MR, Abdel-Wahab O, Andritsos LA, Banerji V, Barrientos J, Blachly JS, Call TG, Catovsky D, Dearden C, Demeter J, Else M, Forconi F, Gozzetti A, Ho AD, Johnston JB, Jones J, Juliusson G, Kraut E, Kreitman RJ, Larratt L, Lauria F, Lozanski G, Montserrat E, Parikh SA, Park JH, Polliack A, Quest GR, Rai KR, Ravandi F, Robak T, Saven A, Seymour JF, Tadmor T, Tallman MS, Tam C, Tiacci E, Troussard X, Zent CS, Zenz T, Zinzani PL, Falini B. 2017. Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia. *Blood* ; 129(5): 553-560.

Else M, Dearden CE, Matutes E, Garcia-Talavera J, Rohatiner AZ, Johnson SA, O'Connor NT, Haynes A, Osuji N, Forconi F, Lauria F, Catovsky D. 2009. Long-term follow-up of 233 patients with hairy cell leukaemia, treated initially with pentostatin or cladribine, at a median of 16 years from diagnosis. *Br J Haematol* ; 145(6): 733-740.

Sigal DS, Sharpe R, Burian C, Saven A. 2010. Very long-term eradication of minimal residual disease in patients with hairy cell leukemia after a single course of cladribine. *Blood* ; 115(10): 1893-1896.

Chihara D, Kantarjian H, O'Brien S, Jorgensen J, Pierce S, Faderl S, Ferrajoli A, Poku R, Jain P, Thompson P, Brandt M, Luthra R, Burger J, Keating M, Ravandi F. 2016. Long-term durable remission by cladribine followed by rituximab in patients with hairy cell leukaemia: update of a phase II trial. *Br J Haematol* ; 174(5): 760-766.

Else M, Dearden CE, Matutes E, Forconi F, Lauria F, Ahmad H, Kelly S, Liyanage A, Ratnayake V, Shankari J, Whalley I, Catovsky D. 2011. Rituximab with pentostatin or cladribine: an effective combination treatment for hairy cell leukemia after disease recurrence. *Leuk Lymphoma* ; 52 Suppl 2: 75-78.

Chihara D, Arons E, Stetler-Stevenson M, Yuan CM, Wang HW, Zhou H, Raffeld M, Xi L, Steinberg SM, Feurtado J, James L, Wilson W, Braylan RC, Calvo KR, Maric I, Dulau-Florea A, Kreitman RJ. 2020. Randomized phase II study of first-line cladribine with concurrent or delayed rituximab in patients with hairy cell leukemia. *J Clin Oncol* ; 38(14): 1527-1538

Figure 1. ^{18}F-FDG PET/CT at diagnosis (A) and two months after treatment including cladribine and rituximab (R) (B).

A: PET scan at diagnosis revealing multiple hypermetabolic lesions: vertebral body of C3, right pedicle of T3, left vertebral hemicorps of T4, pedicle junction and left blade of T8, left acromion, bone lysis both of humeral heads, the two cotyls, coccygeal region, left internal tibial plateau and both femoral heads, femoral necks, per-trochanteric regions, great trochanters, femoral diaphysis. B: follow-up PET-scan 8 weeks after immuno-chemotherapy demonstrating metabolic response with decreased uptake of the multiple metastatic lesions.

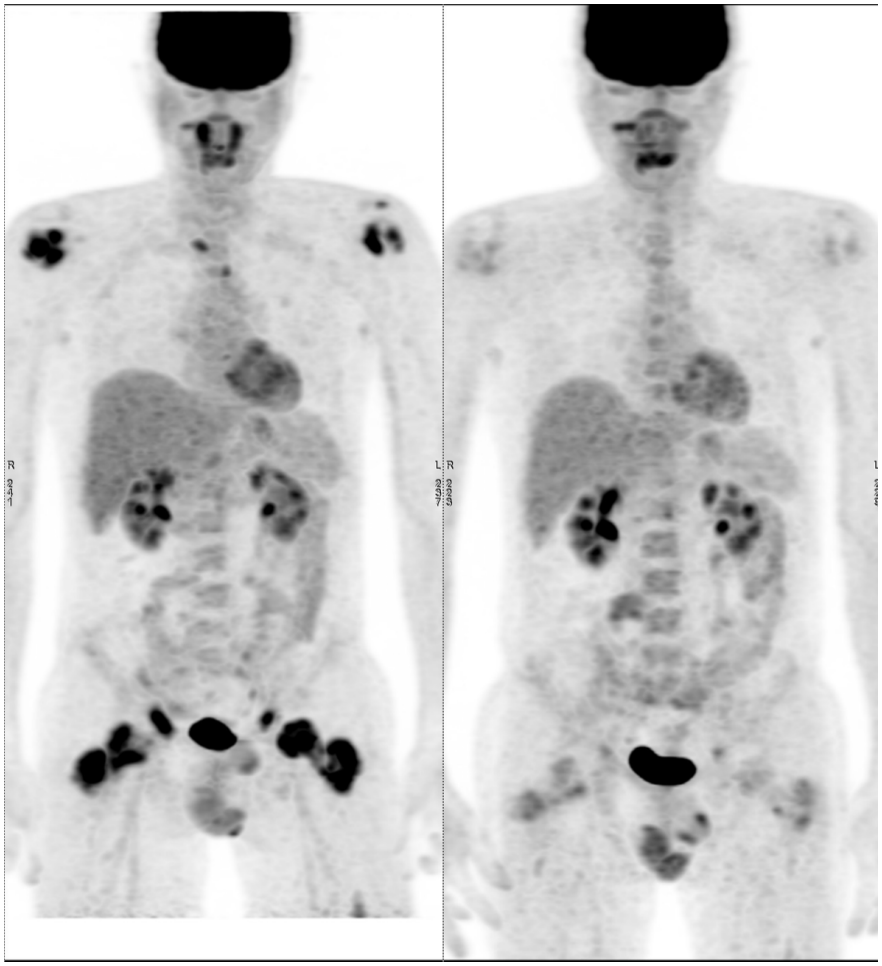

Figure 2. Right femur biopsy. A: Immunochemical studies, showing CD20 positive cells (magnification: x20), B: Abnormal lymphoid cells presenting the $BRAF^{V600E}$ mutation, C: Strong expression of surface Annexin-A1 by the abnormal lymphoid cells and D: Positive expression of DBA44.