Case Report
Transformation of follicular lymphoma in the retroperitoneal muscles demonstrated by CT-guided needle biopsy of FDG-avid lesions; case series

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Abstract: We herein report two cases of relapsed follicular lymphoma (FL) with transformation in the retroperitoneal muscles. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) combined with computed tomography (CT) showed high uptakes in the retroperitoneal muscles. We considered excisional biopsy at first, since it is definitely the most reliable means to obtain histological diagnosis. However, excisional biopsy of the retroperitoneal muscles is challenging for anatomical reasons. Moreover, our patients were kept under poor performance status. Thus, CT-guided percutaneous needle biopsy of FDG-avid retroperitoneal muscles was performed. Histopathological examination of the biopsied specimens demonstrated proliferation of transformed large B cells in both cases. Sheets of large B cells were also recorded in one case. CT-guided needle biopsy is less prioritized than excisional biopsy because of limited information on tissue architecture and increasingly complicated WHO classification. Our series indicate that image-guided needle biopsy of FDG-avid lesions is sufficient for the diagnosis of transformation. Higher priority should be given to this method in the setting of transformed aggressive lymphoma.

Keywords: Follicular lymphoma, transformation, retroperitoneum, FDG-avid, CT-guided needle biopsy

Introduction
Transformation of an indolent lymphoma to a more aggressive subtype is a recurrent phenomenon, among which that of follicular lymphoma (FL) into diffuse large B-cell lymphoma is most frequent. The cumulative incidence of transformation in the course of FL has been reported as 10-60% [1-6]. The differences in incidence rates are partly explained by the differences in the median follow-up period. Furthermore, the criteria for transformation are not uniform among the studies. Some reports include only histological transformation such as loss of the follicular architecture and sheets of large cells on microscopic examination. Others allow for clinical transformation including rapid disease progression, development of systemic symptoms, and rapid increase in serum lactate dehydrogenase (LDH) level. Moreover, the policy regarding autopsy and re-biopsy on relapsed or progressive disease fundamentally affects the incidence rate. According to an autopsy series, transformation was recorded in up to 70% of patients with FL [7].

Excisional biopsy is the most reliable means to obtain histological evidence of transformation. However, it frequently requires surgery under general anesthesia for anatomical reasons. Moreover, this method cannot be applied to heavily treated patients who are kept under poor performance status. We herein report two cases of relapsed FL with transformation in the retroperitoneal muscles. Histological transformation was proven by CT-guided percutaneous needle biopsy of fluorodeoxyglucose (FDG)-avid lesions.

Case reports
Case 1
A 77-year-old female presented with edema of the lower legs. Physical examination was nota-
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Her hemoglobin level was 114 g/L, leukocyte count 4.0×10⁹/L with 24% lymphoid cells, and platelet count 176×10⁹/L. Other laboratory findings included increased LDH and soluble interleukin-2 receptor (sIL-2R) levels of 364 IU/L and 4,123 U/mL, respectively. CT scan detected paraaortic lymphadenopathy compressing the urinary tracts and resultant bilateral hydronephropathy. Microscopic examination of an excised inguinal node led to the diagnosis of FL grade 1. Immunophenotype of the lymphoma cells was CD3-, CD5-, CD10+, CD20+, CD79a+, Bcl-2+ and Bcl-6+. Ki67 positivity was 10-20%. Epstein-Barr virus encoded RNA-1 in situ hybridization gave a negative result. Bone marrow examination also identified lymphoid cells of the same immunophenotype. Initial treatment with six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) regimen resulted in complete remission. Six months later, she presented with postrenal failure and edema of the lower legs. CT scan indicated regrowth of the paraaortic nodes with hydronephropathy. Several different salvage regimens were administered with limited efficacy. At last, the patient developed weakness of the right quadriceps muscles due to femoral nerve palsy. CT scan without contrast enhancement...
revealed thickening of the iliacus muscles. F-18 FDG-positron emission tomography (PET) combined with CT (FDG-PET/CT) scan was notable for diffuse uptakes in the iliacus muscles with maximal standardized uptake value (SUV max) of 19.5 (Figure 1A). CT-guided percutaneous needle biopsy of the right iliacus muscle was then performed to obtain histological evidence (Figure 1B). Microscopic examination of the biopsied specimen identified proliferation of large B cells (Figure 2). Taken together, we concluded that histological transformation had occurred in the iliacus muscles. Palliative local radiotherapy to the right iliacus muscle at a total dose of 30 Gy in 10 fractions yielded transient amelioration of the right femoral nerve palsy with mild myelosuppression (Grade 1 according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events version 4.0). The patient succumbed to death 6 months later due to progressive disease. Autopsy disclosed sheets of large B lymphocytes in the iliacus muscles. Immunophenotype of the large cells was CD10+, CD20+, CD79a+ with Ki67 positivity of 70-90%.

Case 2

Another 77-year-old female presented with malaise, shoulder pain, and left cervical lymphadenopathy. Laboratory data were remarkable for leukocyte count of 4.9×10^9 /L with 33% lymphoid cells, LDH level of 270 IU/L, and sIL-2R level of 8,705 U/mL. Histopathology of a biopsied left cervical node was consistent with FL of grade 3a. Immunohistochemistry showed that the lymphoma cells were positive for CD19, CD20, CD10, Bcl-2 and deviated immunoglobulin light chain expression. CT scan revealed generalized lymphadenopathy and mild splenomegaly. Initial treatment with seven cycles of R-CHOP regimen led to complete remission. Five months later, she began to complain of right thigh pain, consistent with the area innervated by the femoral nerve. Abdominal CT without contrast enhancement showed thickening of the right iliacus and psoas major muscles. FDG-PET/CT scan showed diffuse uptakes in the muscles with SUV max of 13.7 (Figure 1C, 1D). CT-guided percutaneous needle biopsy of the right psoas major muscle was conducted. Histopathology of the biopsied specimen confirmed sheets of large B lymphocytes (Figure 3). Fluorescence in situ hybridization (FISH) analysis detected BCL2/IgH fusion and BCL6 gene rearrangement (Figure 4). Comprehensively, the patient was diagnosed with histological transformation in the retroperitoneal muscles. Her symptoms were unresponsive to salvage immunochemotherapy. Palliative local radiotherapy was then administered to the retroperitoneal muscles at a total dose of 30 Gy in 10 fractions, which resulted in partial pain relief without adverse events including myelosuppression.

Discussion

Our cases were featured by disturbances of the femoral nerve. The femoral nerve descends through the psoas major muscle and anterior to the iliacus muscle. Involvement of these retroperitoneal muscles is therefore associated with femoral nerve dysfunction, which in turn causes sensorimotor symptoms of the thigh such as weakness of the quadriceps muscles in Case 1 and thigh pain in Case 2. We should suspect infiltration to the retroperitoneal muscles when patients exhibit disturbances of the femoral nerve. As for treatment, the symptoms were transiently relieved by palliative local radiotherapy with minimal hematological toxicity.

Semi-quantitative measurements of FDG uptakes are useful in distinguishing indolent from aggressive lymphomas. A retrospective study showed that all cases of indolent lymphoma.
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ma had an SUV ≤ 13 and that SUV > 10 excluded indolent lymphoma with a specificity of 81% [8]. Similarly, appearance of a high FDG uptake in the background of indolent lymphoma suggests transformation. In one study, aggressive lymphoma developing from FL grade 1 (n=8), 2 (n=9), and 3 (n=3) indicated the mean SUV max of 19, 16, and 19, respectively [9]. Our cases also showed high FDG uptakes with SUV max of 19.5 and 13.7, which was consistent with the prior results.

One may ask whether histological evidence is still required for FDG-avid lesions with high SUV. The diagnosis of transformed aggressive lymphoma fundamentally affects the subsequent treatment strategy including the choice of autologous stem cell transplant. Moreover, the correlations between FDG avidity and histopathology have not so far been fully elucidated. We should therefore try to obtain histological evidence whenever possible. CT-guided percutaneous needle biopsy is less invasive than excisional biopsy. The diagnostic accuracy of image-guided needle biopsy for malignant lymphoma has been reported as 78-87% [10-13]. Nevertheless, evaluation by needle biopsy is still given relatively low priority due to limited information on tissue architecture and increasingly complicated subclassification of malignant lymphoma by the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues. In our series, CT-guided percutaneous needle biopsy of FDG-avid retroperitoneal muscles was performed not only because excisional biopsy of the lesion requires surgery under general anesthesia but also because our patients carried poor performance status. Microscopic examination of the biopsied specimens demonstrated proliferation of transformed large B cells in both cases.

The initial diagnosis of malignant lymphomas indeed requires detailed information on tissue architecture. In contrast, the diagnosis of transformation in the course of indolent lymphomas is supported by proliferation of large lymphoma cells and thus is less dependent on architecture. FISH analysis using needle biopsy specimens also provides additional information. Hence, image-guided needle biopsy is thought to be useful for the diagnosis of transformation. This method can save surgical procedures and time to treatment.

In conclusion, CT-guided needle biopsy of FDG-avid lesions should be given higher priority in the diagnosis of transformation.

Disclosure of conflict of interest

None.

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