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Case Report
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Non-Hodgkin Lymphoma Secondary to Hodgkin Lymphoma in an Adult Patient With Nijmegen Breakage Syndrome

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Nijmegen breakage syndrome (NBS) is a rare inherited autosomal recessive DNA repair disorder characterized by microcephaly, growth and mental retardation, immunodeficiency, radiation hypersensitivity, and increased incidence of lymphoid malignancies.[1] Nijmegen breakage syndrome is characterized by a 5-bp deletion on exon 6 in the NBN (formerly NBS1) gene[2] on chromosome 8q21. The hypomorphic mutation leads to expression of a truncated and insufficiently functioning protein (p70-Nibrin) with a 26-kDA N-terminal and a 70-kDa fragment.[3] Nibrin forms a complex with MRE11 and RAD50 (MRN), which is involved in processing DNA double-strand breaks.[4] Thus, dysfunctional nibrin leads to impaired cellular DNA damage response. Consequently, NBS patients harbor an increased risk of developing hematological malignancies and are extremely vulnerable to ionizing radiation (IR). So far mostly pediatric NBS patients have been described, since lymphoid malignancies are often fatal before adulthood.

To our best knowledge, we here report on diagnostic procedures and therapy of the first adult NBS patient with a non-Hodgkin lymphoma (NHL) secondary to a successfully treated classical Hodgkin lymphoma (cHL) who achieved a second complete remission (CR).

The patient had been diagnosed with NBS at birth and had been registered in the NBS Registry (patient no. 45). In 2011, the patient was diagnosed with stage IV nodular sclerosis cHL and treated with a tailored regimen of chemotherapy in our Hematology/Oncology Department. The CR was achieved after 4 cycles of attenuated chemotherapy. At onset of disease and during successive cHL treatment very severe complications including liver failure, kidney failure, and fungal sepsis occurred. A detailed report on the clinical course, complication management, and treatment procedures of the patients cHL was previously published by Engel et al.[5] During 5 years of follow-up, he remained in CR with completely restored liver and kidney function.

Five years and 2 months after treatment for cHL, the now 29-year old patient was admitted to our hospital with severe dysphonia, dyspnea, 15 kg weight loss in 6 months and recurrent fever. Two weeks earlier the patient presented himself to a primary care hospital with coughing, fever, and leg pain. At this time serum chemistry showed abnormalities for lactate dehydrogenase (LDH) (298 U/L), C-reactive protein (CRP) (11.5 mg/dL), uric acid (8.7 mg/dL), and D-dimer (1.58 mg/dL). The patient was discharged with symptomatic treatment suspecting viral infection. No imaging diagnostics was performed at that time.

On admittance to our hospital, serum analysis showed an elevated LDH (444 U/L), uric acid (8 mg/dL), and CRP elevation (27.7 mg/dL). Clinical examination revealed cervical and supraclavicular lymphadenopathy and left vocal cord paresis, highly suspicious for relapse of cHL. In order to avoid harmful IR, combined (F-18)-fluorodeoxyglucose (FDG) positron emission tomography/magnetic resonance imaging (PET/MRI) was used for initial staging. PET/MRI revealed FDG uptake in masses predominantly in the left hemithorax, mediastinum, and supraclavicular lymph nodes. In addition, 2 smaller infradiaphragmal lymph nodes below the gastro-esophageal passage, as well as intrapulmonary masses were seen (Fig. 1A–C). An FDG-positive cervical lymph node was surgically removed to verify the suspected relapse of the patients' previous cHL. However, histopathological examination showed a diffuse proliferation of medium-sized centroblastic lymphoid cells with high proliferative activity (80% Ki-67 positivity). Hodgkin-like or Reed-Sternberg-like giant cells were not observed. Immunohistochemically the tumor cells were strongly positive for CD20 and Pax5 with co-expression of Bcl6 and MUM-1, but negativity for CD5, CD23, Cyclin D1, CD30, CD23, and EBV. Thus, the diagnosis of a diffuse large B-cell lymphoma (DLBCL), not otherwise specified was established (Fig. 2A–D). The diagnosis of an aggressive B-cell NHL was consistent with the severe symptoms of the patient. Histological examination of the bone marrow biopsy showed no signs of infiltration of the DLBCL. The differentiation of cHL

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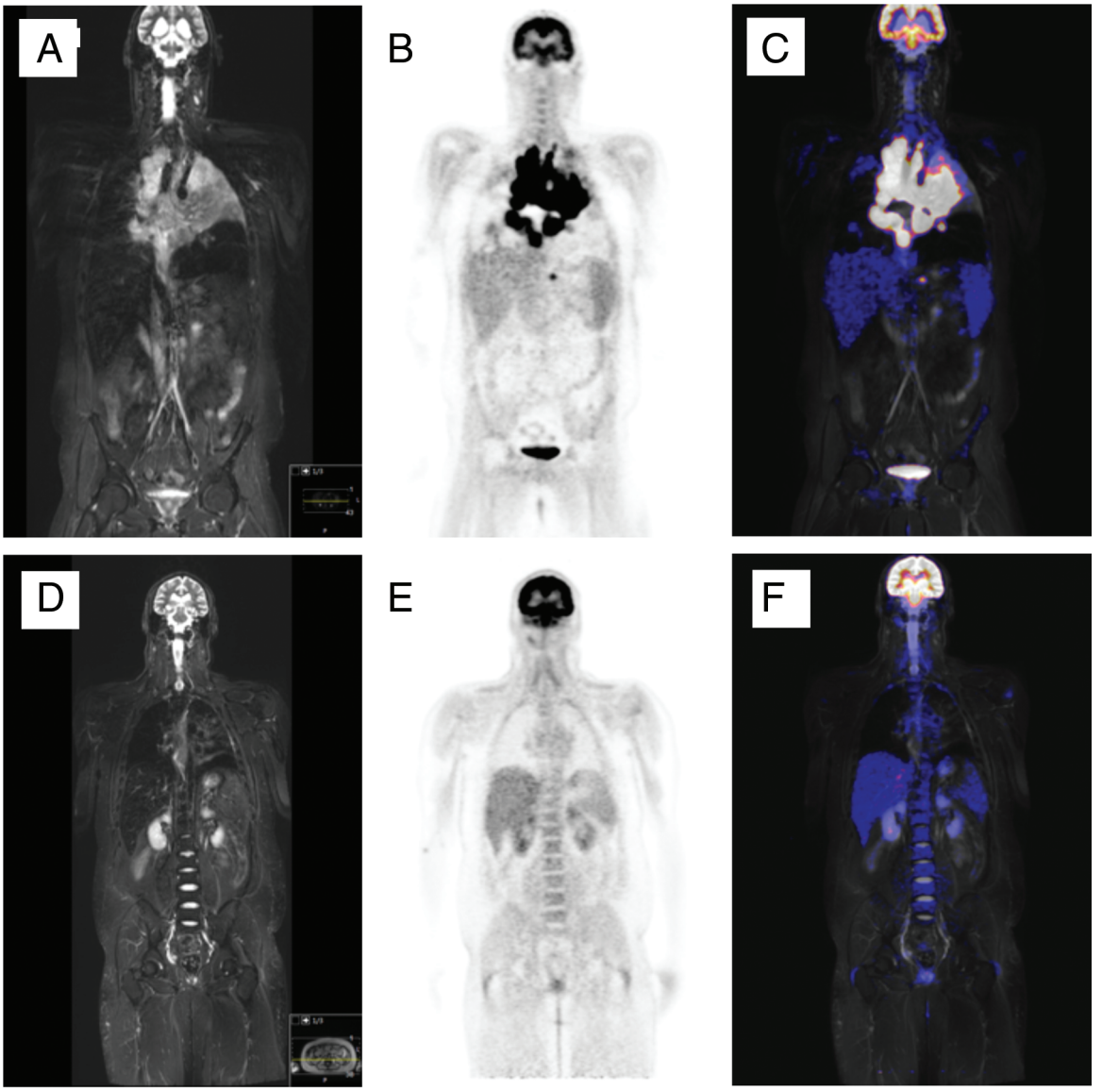

Figure 1. Positron emission tomography (PET)-magnetic resonance imaging was used to reduce ionizing radiation considering the patient's underlying DNA repair disorder. Representative coronary images (A, D: STIR; B, E: PET; C, F: Fusion) are shown before (upper row) and after (lower row) 6 cycles of chemotherapy. STIR = short inversion time inversion recovery.

from conventional DLBCL was straightforward by morphology and easily confirmed by immunohistochemistry. Based on these findings, we concluded that the DLBCL was most likely a secondary lymphoma. In summary, this NBS patient presented with a stage IVB DLBCL after previous treatment for stage IV cHL.

Treatment was initiated with a prephase of 40 mg dexamethasone daily, which led to rapid regression of the dyspnea and dysphonia. The patient's history of severe infectious complications and organ failure during previous treatment, resulting in a prolonged intensive care unit hospitalization, in addition to the highly increased risk of subsequent secondary malignancies due to previous genotoxic chemotherapy led us to decide on an attenuated Rituximab-CHOP regimen (Rituximab 375 mg/m^2 day 1; 50% reduction of standard dose doxorubicin and cyclophosphamide; vincristine 2 mg total in cycle 1, then 1 mg; prednisolone 100 mg day 1–5). Extended antibiotic and antifungal infection prophylaxis with cotrimoxazole 960 mg 3 times per week, valaciclovir 500 mg twice daily, and posaconazole 300 mg once daily was administered. During neutropenia, the patient also received ciprofloxacin 500 mg twice daily as antibiotic prophylaxis. The first cycle of chemotherapy was given in a monitored setting, and PEGylated granulocyte colony-stimulating factor was injected on day 4 to shorten the duration of neutropenia. Cycle 2 until 6 were administered in an outpatient setting every 3 weeks, with frequent visits and continued broad prophylaxis. Two additional rituximab 375 mg/m^2 were administered, after an additional 3 and 6 weeks. Under intensified prophylaxis and clinical monitoring, no major complications occurred. PET/MRI upon treatment completion revealed a CR (Fig. 1D–F) according to Lugano criteria.[6] Follow-up after 3, 6, 9, and 12 months shows an ongoing CR. The MRI after 12 months showed mediastinal and hilar lymphadenopathy. Biopsy was performed using video-guided thoracoscopy. Histopathological examination showed chronic inflammation but no signs of neoplasia. Thus, the patient is in ongoing biopsy-proven CR.

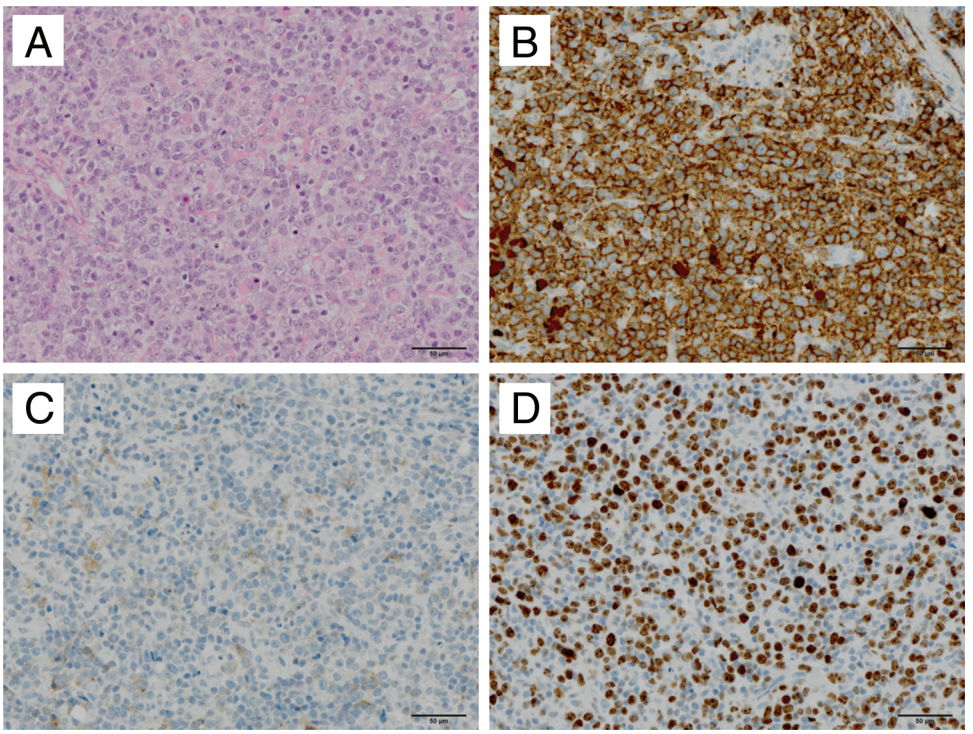

Figure 2. Lymph node biopsy consisted with the diagnosis of a diffuse large B-cell lymphoma, not otherwise specified. (A) Hematoxylin and eosin staining. (B) CD20 immunohistochemistry. (C) CD30 immunohistochemistry. (D) MIB staining showing a high proliferation rate (80%). MIB = molecular immunology borstel.

The NBS is a rare DNA repair disorder frequently resulting in childhood death, often due to lymphoid malignancies, which remain the leading cause of death in these patients.[7] Development of secondary neoplasms is a known, in most cases fatal complication. More data and prospective studies are needed to further improve treatment for malignancies in NBS patients. So far only few cases of pediatric NBS patients with secondary malignancies have been reported and specific data are scarce.[7,8] Clinical management and diagnosis in cancer patients with DNA repair disorders such as NBS is challenging and severe infectious complications occur frequently during treatment. Early evaluation of immune state seems to be important for such patients since the immune deficiency appears to be heterogeneous, ranging from insignificant to severe. In the patient described here, no severe infectious complications occurred before the first lymphoma occurrence. However, on cHL onset and during initial therapy he suffered from grade IV fungal sepsis, while no life-threatening infections occurred after. Therefore, we assumed that our patient's immune response was not severely impaired, even though we knew he suffered from selective IgG4 deficiency at birth. This led us to perform aggressive therapy for a second time. We demonstrate that the use of an individualized regimen of standard immunochemotherapy under extended prophylaxis and monitoring was feasible and resulted in a second CR in this patient with a DNA repair disorder. High susceptibility to IR in these patients makes diagnosis difficult as conventional imaging is contraindicated. The availability of PET/MRI may substantially improve the diagnostic work up since it provides functional imaging without the risk of applying avoidable DNA damage. Similar performance of FDG-PET/MRI for lymphoma diagnosis compared to standard FDG-PET/computed tomography has been reported.[9] Here we illustrate that PET/MRI can be used as a reliable lymphoma staging tool for patients with DNA repair disorders.

New approaches for treating cancer in DNA repair disorders patients are needed since chemotherapy further increases risk of secondary malignancies and radiotherapy is contraindicated. Hematopoietic stem cell transplantation can be considered in NBS patients with hematopoietic malignancies and/or severe immunodeficiency, but has so far mostly been performed in younger patients.[10] Multicenter prospective studies for lymphoma treatment in NBS patients are, however, lacking to define standards of care.

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