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Predisposition to hematologic malignancies in patients with xeroderma pigmentosum

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Germline predisposition is a contributing etiology of hematologic malignancies, especially in children and young adults. Germline predisposition in myeloid neoplasms was added to the World Health Organization (WHO) 2016 classification(1), and current management recommendations emphasize the importance of screening appropriate patients(2). Rare syndromes of DNA repair defects can lead to myeloid and/or lymphoid neoplasms(3). Here, we describe our experience with hematologic neoplasms in the defective DNA repair syndrome, xeroderma pigmentosum (XP), including myelodysplastic syndrome (MDS), secondary acute myeloid leukemia (AML), high-grade lymphoma, and an extremely unusual presentation of mixed phenotype acute leukemia (MPAL) with B, T and myeloid blasts.

XP is a rare, autosomal recessive, nucleotide excision repair (NER) disorder, characterized by failure to repair ultraviolet radiation-induced and other DNA damage. XP arises from mutations in the DNA repair/transcription genes *XPA*, *ERCC3/XPB*, *XPC*, *ERCC2/XPD*, *DDB2/XPE*, *ERCC4/XPF/FANCO* and *ERCC5/XPG*, or in the bypass polymerase, *POLH/XPV*(4). Many cancers of the skin and sun-exposed mucous membranes develop in childhood(4-6), and about 25% of patients develop progressive neurologic degeneration. XP is considered a disorder of premature aging with associated skin changes, sensorineural deafness and accelerated neuronal loss. As vigilance in skin cancer prevention, diagnosis and management has extended the life expectancy of patients with XP, other premature aging features are being identified, including premature menopause(7) and internal cancers. Internal malignancies in XP, primarily of the central nervous system, occur with an estimated ten- to twenty-fold increased incidence compared to the general population(5). Isolated cases of MDS and/or acute leukemia have previously been reported((5, 8) and cited in(9)). Most recently, the occurrence of MDS and

secondary AML has been described(9) in patients with a frequent North African *XPC* founder mutation c.1643-1644delTG, resulting in a frameshift mutation in exon 9.(10)

To study the natural history of XP, a cohort of 117 patients and their families were enrolled at the National Institutes of Health (NIH) from 1971 to 2018(6). This study was approved by the NCI institutional review board, and informed consent was obtained for all participants. Mutation testing in XP associated genes was performed by polymerase chain reaction (PCR) and Sanger sequencing. Within this cohort of 117 XP patients, 65 were identified with mutations in *XPC*, including 3 patients with homozygous *XPC* c.1643-1644delTG, a North African founder mutation, and 2 with compound heterozygous *XPC* c.1643-1644delTG.(11, 12)

Four patients in our cohort developed hematologic neoplasms, including MDS, acute leukemias, and high-grade lymphoma (Table 1), and all four had germline mutations in *XPC*. None of the four had received prior systemic chemotherapy or reported a family history of hematologic neoplasms. The North African founder mutation c.1643-1644delTG was homozygous in two of these patients and compound heterozygous in one patient. The fourth patient had a homozygous mutation affecting a splice site, c.622 -2A>C. There were two additional patients with the founder mutation in this cohort, XP394BE homozygous(12), and XP132BE compound heterozygous(11), and they developed basal and squamous cell carcinomas but no internal cancer by age 29 years and 9 years, respectively.

Case XP540BE. This patient had a highly unusual presentation of MPAL. She was diagnosed with XP at age 18 months with numerous lentigines on sun-exposed skin, when her family emigrated from Morocco to the United States. The homozygous North African *XPC* founder mutation was present(10). She had her first skin cancer at age 8, and subsequently developed more than 40 cutaneous basal and squamous cell carcinomas, one melanoma in situ,

and one ocular surface squamous neoplasm. She was diagnosed with a multinodular goiter at age 9 years 8 months, with several complex nodules leading to removal of her thyroid gland. Histopathology showed multinodular adenomatous/papillary hyperplasia. At age 19, she presented with night sweats, fatigue, and lymphadenopathy. Laboratory studies revealed pancytopenia with hemoglobin 6.8 g/dL, platelet count 84,000/ μ L, and white blood cell count 1,750/ μ L with 18.2% blasts. Complete blood counts three years prior had been normal. Review of the peripheral blood smear showed intermediate-sized blasts, and flow cytometry indicated a diagnosis of MPAL, with the presence of three heterogenous blast populations: B/myeloid (TdT+, CD19+, CD79++, CD22+, MPO+, CD13+, CD33+), T/B/myeloid (TdT+, cCD3+, CD7++, MPO dim, CD13+, cCD79 dim) and T/B blasts (TdT+, cCD3++, CD7++, cCD79a dim). Bone marrow biopsy demonstrated 90% overall cellularity with near complete replacement of normal hematopoiesis by small to medium blasts. Cytogenetics and FISH panel were normal. No clonal T cell receptor or immunoglobulin rearrangements were detected. Treatment was initiated on Children's Oncology Group protocol AALL1131 (ClinicalTrials.gov Identifier: NCT02883049), which includes induction with vincristine, daunorubicin, PEG-asparaginase, prednisone, intrathecal cytarabine and intrathecal methotrexate; followed by consolidation with vincristine, subcutaneous cytarabine, 6-mercaptopurine, cyclophosphamide, PEG-asparaginase, and intrathecal methotrexate. Complete remission was achieved, and the patient remains alive at age 21.

Case XP393BE. Patient XP393BE, from Northern Africa, had an extensive history of skin cancer that has been previously described, but no other malignancy(12). He had the homozygous North African *XPC* founder mutation. At age 29, he was diagnosed with diffuse large B cell lymphoma, stage IV. He started treatment with rituximab, cyclophosphamide,

doxorubicin, vincristine, and prednisone (R-CHOP). After 1 cycle, he declined further chemotherapy treatment and elected to enroll in hospice. This patient had one brother (XP394BE), also homozygous for the North African *XPC* founder mutation, who had basal and squamous cell carcinomas of the skin but no internal cancers and was alive at age 28 years without hematologic abnormality.(12)

Case XP30BE. Patient XP30BE, from the United States, was diagnosed with XP with the presence of compound heterozygous mutations in *XPC* (c.1643-1644delTG and c.1103-1104delAA).(11) Over 200 skin cancers were treated previously. At age 36 years, he was diagnosed with MDS with complex karyotype as listed in Table 1, and later progressed with secondary AML at age 38. Molecular profiling was not performed. He received treatment with decitabine without reported unexpected treatment toxicities, as well as supportive care. The patient died at age 38 with progressive disease.

Case XP243BE. Patient XP243BE, from the US, had a diagnosis of XP with history of 10 skin cancers. A homozygous *XPC* mutation c.622 -2A>C affecting a splice site was present. At 18 years old, he was diagnosed with MDS with complex karyotype, described in Table 1. He underwent hematopoietic stem cell transplant at age 20 with a myeloablative conditioning regimen of fludarabine, busulfan 0.8mg/kg/dose every 6 hours for 16 doses, anti-thymocyte globulin without total body irradiation, and graft-versus-host disease prophylaxis with cyclosporine and methylprednisolone. His course was complicated by cardiac dysfunction, acute renal insufficiency, sepsis, and fatal diffuse alveolar damage two weeks following transplant.

Splice site mutations at position c.622-2A were present in four other patients in the NIH cohort. Two who were heterozygous for *XPC* c.622 -2A>C had multiple skin cancers but no internal malignancy. Patient XP23BE of Native American ancestry was homozygous for c.622 -

2A>C,(11) developed a spinal cord astrocytoma(13) and died of metastatic melanoma at age 31. Patient XP24BE of US and Hungarian ancestry had c.622 -2 A>G (11) and died of glioblastoma at age 35(14). Additional risk for non-cutaneous malignancies may be present in this patient group.

Heightened clinical suspicion for hematologic malignancies is warranted for patients with XP. The North African *XPC* founder mutation in particular is associated with risk of not only MDS/AML, but also high-grade lymphoma and mixed phenotype acute leukemia. Sarasin et al. reported a several thousand-fold increased frequency (8%) of MDS and AML in XP patients of North African descent carrying the *XPC* founder mutation c.1643-1644delTG, and prior case reports of XP patients with hematologic malignancies have also been limited to patients with well-described mutations in *XPC* and/or North African descent.(9) Three of the 4 patients with hematologic malignancies in our series (Table 1) carried the founder mutation, and they represent 60% of our cohort of five XP patients with the founder mutation. In addition, in our series we also found risk of hematological malignancy due to a splice site mutation in *XPC* (c.622 -2A>C). The genetic profiles in the two patients with MDS and secondary AML described here included complex cytogenetics with classical MDS/AML abnormalities of monosomy 7 and monosomy 5. The spectrum of hematologic malignancies in XP extends beyond MDS and AML to include mixed phenotype leukemia and high-grade lymphoma. Diffuse large B cell lymphoma is a common hematologic malignancy with expected incidence of 5.1 per 100,000 persons, but the young age of our patient is unusual with only 6.7% of cases occurring at less than age 35 (Seer 21 2012-2016, <https://seer.cancer.gov/statfacts/html/dlbcl.html>, accessed 6/26/2019). In contrast, hematologic malignancies have not been strongly associated with somatic mutations in XP associated genes, with only rare occurrence of reported *XPC* mutations in the Genomic Data

Commons Data Portal (<https://portal.gdc.cancer.gov/>) (1 reported simple somatic mutation in lymphoma and 1 in myeloid leukemia).

Rare syndromes of DNA repair defects associated with myeloid and/or lymphoid neoplasms(3) include Fanconi anemia, Bloom syndrome (*BLM*), Werner syndrome (*WRN*), Rothmund-Thomson syndrome (*RECQL4*), Nijmegen Breakage Syndrome (*NBN*), Ataxia Telangiectasia (*ATM*), Ligase IV syndrome (*LIGIV*) and constitutional DNA mismatch repair disorders (*PMS2*, *MLH1*, *MSH2*, *MSH6*, *EPCAM*). In contrast to other germline predisposition syndromes, XP is not typically associated with immunodeficiency, cytopenias, or platelet dysfunction. A notable exception is certain mutations in *ERCC4/XPF/FANCO* that cause defects in DNA interstrand crosslink repair. Patients with mutations in *ERCC4* have been described with clinical manifestations of Fanconi anemia(15), but these features have not been reported in patients with *XPC* mutations.

Management of hematologic malignancies in patients with defective DNA repair pathways requires careful consideration. Consensus management guidelines have been developed for Fanconi anemia and telomeropathies(2), but are not yet developed for other DNA repair syndromes. While patients with XP generally tolerate diagnostic X-rays and radiotherapy, sensitivity to certain chemotherapies depends on the specific NER deficiency. Transcription-coupled NER, which repairs intrastrand DNA crosslinking adducts formed by agents such as cisplatin, is deficient in mutations affecting *XPA*, *ERCC2/XPD*, *ERCC5/XPG* and *ERCC4/XPF/FANCO*.(16) In contrast, mutations in *XPC* cause a selective deficit in global-genome NER, but transcription-coupled NER remains intact without apparent increase in cisplatin sensitivity.(16) A case report has been published describing an XP patient who tolerated AML induction chemotherapy and transplant conditioning regimens, which included

anthracycline, cytarabine, fludarabine, busulfan and cyclophosphamide, without unusual toxicities.(8) Prior experience with hematopoietic stem cell transplantation in this patient population is limited to a reported case(8) and a recently published cohort.(9) The appropriate considerations for donor selection, conditioning regimens, graft-versus-host disease prophylaxis, and risk of aggressive immunosuppression-associated skin malignancies are unknown, and sensitivity to certain chemotherapy agents depends on the specific NER deficiency. Care for these patients will benefit from the evolving experience in surveillance and management of patients with genetic predisposition to hematologic malignancies(2) and early referral to transplant centers with this expertise.

Within the WHO 2016 classification framework, hematologic neoplasms in XP patients would be consistent with “myeloid neoplasms with germline predisposition and other organ dysfunction” with lymphoid neoplasms also reported. It would be reasonable to consider monitoring XPC patients for hematologic and central nervous system malignancies, particularly those carrying the c.1643-1644delTG or the c.622 -2A>C splice mutation.

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Table1 - HEMATOLOGIC MALIGNANCIES IN A COHORT OF PATIENTS WITH XERODERMA PIGMENTOSUM AT NIH

ID	SEX	XP MUTATIONS	AGE (YEARS) AT DIAGNOSIS OF HEMATOLOGIC MALIGNANCY/DEATH	HEMATOLOGIC DISORDER	BONE MARROW KARYOTYPE
XP243BE	M	homozygous <i>XPC</i> c.622 -2A>C _{1,2}	18/20	Myelodysplastic syndrome	44, XY, -3, i(5)(p10), del(6)(p21), t(6;7)(p10;p10), -7,add(7)(p22), -8, del(9)(q21.2), add(10(p15), -22,+mar1, +mar2[15]/46, XY[5]
XP393BE(10)	M	homozygous <i>XPC</i> c.1643-1644delTG _{1,2}	29/29	Diffuse large B-cell lymphoma, stage IV	Not available
XP30BE(11)	M	compound heterozygous <i>XPC</i> c.1643-1644delTG ₁ <i>XPC</i> c.1103-1104delAA ₂	36/38	Myelodysplastic syndrome; progression to secondary AML	39-47, XY, add(1)(p34)[9], add(1)(q21)[8], -5[8], -7[9], -8[8], -9[3],+11[12], del(12)(p12)[10] -13[4], -14[5], -15[10], -16[9], -17[3], -18[6], -22[3], -Y[3], +0-4mar[cp12]
XP540BE	F	homozygous <i>XPC</i> c.1643-1644delTG _{1,2}	19/Alive at 21	Mixed phenotype acute leukemia	46, XX[20]