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Case Report
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X Linked Lymph Proliferative Disease-1 (Xlp-1), Reporting Patients Series from Palestine

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Abstract

Primary immune deficiency diseases are rare diseases worldwide. These are difficult diseases and often are deadly if not recognized and treated early. Things are even worse when your practice is in a developing country in which you lack the diagnostic and the therapeutic interventions. Since most of these diseases are autosomal recessive diseases, consanguinity play a major cause of increasing the incidence of these diseases.

Consanguinity is Common in Palestine

X linked inheritance is also common in these illnesses. Both types of inheritance put a social burden on the families, but X linked inheritance of such diseases put an extreme stress on the family and on the female carrier in particular. In addition to consanguinity, these social stresses participated significantly in increasing the recurrence of the same disease within the same family and consequent increase in the general incidence of the disease. Genetic counseling is usually provided for all parents with genetically mediated disease. But as mentioned above, social stresses on the parents and their families cause failure of this method and recurrence of the same disease several times in the same family. The health care system in Palestine is an evolving one. In Pediatric age, priorities are directed toward primary health care. Thus we lack most of the diagnostic and therapeutic interventions and we depend mainly on Israeli centers for diagnostic work up (flowcytometry, invitro lymphocyte functional assays and genetic diagnostics) and for bone marrow transplantation when indicated. We present our cases of XLP-1, in which diagnosis was made in Palestine and once bone marrow transplant and or chemotherapy for lymphomas were needed, treatment was continued in Hadassah Medical center in Israel. The outcome of this cooperation was excellent XLP-1 In this extended family from Palestine, late in the 1970s, most of the females at risk to be carriers of the disease were studied for EBNA antibodies. Those who had positive EBNA were defined as not carriers. Females who tested negative for EBNA were considered carriers of the disease and did not get married and did not have children. For social reasons, some females were not tested. Their male offspring later developed XLP.

It was late in 1990s when the gene responsible for XLP was identified and the pathogenesis of the disease was described. In which it was proved that SAP (SLAM associated protein) controls SLAM (signaling lymphocyte activating molecule). SLAM is a known inhibitor of lymphocyte proliferation after EBV infection [1-3]. SAP deficiency will cause uncontrolled proliferation of lymphocytes. The mutation in this family (XLPc. 158 T(P.Thr53Ile) was found and used subsequently to define the diseased male and the carrier females. This replaced the old criteria for diagnosis of the disease and the carrier status. Serology (EBNA titer) to define the carrier status of female was considered unreliable.

The known family history of XLP (before we know the gene responsible for the disease) made the diagnosis of these cases easier as will be shown in the description of the cases. Later, depending of genetic diagnostic methods for XLP made things easier to make the diagnosis before the patient encounter EBV infection and subsequent dysgammagblobulinemia and lymphomas. This helped to take therapeutic interventions as will be described.

In this family, we report a male patient with XLP who developed Burkett's lymphoma despite the fact that his EBV by PCR in the blood was negative. Diagnosis was made after the child in the second year of life developed recurrent small intestinal intussusceptions and found during surgical exploration to have Burkett's lymphoma. This should rise up a question if the EBV is the only trigger to develop lymph proliferation and or lymphomas, or there are other factors that cause the disease. Also, we report a case of XLP in which bone marrow transplantation was performed

before the child develops dysgammagblobulinemia and or lymphoma.

Case Description

Family A, 1 patient. Bone marrow transplant was carried out after the child developed Non Hodgkin's lymphoma. At the age of one year, the previously healthy child presented with recurrent otitis media and spleenomegally. This was preceded with prolonged febrile illness. His CBC showed persistent leukocytosis (WBC 20 K) His immunoglobulin levels at age of one year were initially normal Within 3 months the levels of all immunoglobulins (A, M, G and E) all dropped to almost zero. EBV serology as not available to us at that time. His lymphocyte subsets were normal, namely normal CD19 and normal CD4, CD8 and CD56. He tested positive for the mutation XLPc. 158 T(P.Thr53Ile) . He was started on IVIG infusion. He had persistent microcytic anemia. He otherwise did very well until he developed Non Hodgkin's lymphoma at the age of 8 years. Almost 7 years after initial presentation. He was transplanted with 100% matched related bone marrow. He is still in need of IVIG infusion, despite normal in vitru functional assay. Rutiximab was used during preparing him for bone marrow transplant.

Genetic Counseling Was Provided

Family B, the mother is a sister to the mother in family A. We report 2 patients from this family. The first patient had similar presentation of the patient in family A. but he developed Burkett's lymphoma (abdominal) at the age of 2 years, only one year after the diagnosis at the age of 1 year. He was treated initially without bone marrow transplant. 2 years after recovery, he had recurrence of Burkett's lymphoma in the terminal rectum. He presented with intractable diarrhea. The site of recurrence and the recurrence of Burkett's lymphoma was surprising. He was treated again and this time he was transplanted with 100% matched related bone marrow. He developed severe graft versus host disease. His is now healthy and off IVIG infusion.

The second case in family B was diagnosed at the age of 4 months depending on the genetic study for the known mutation. He was transplanted at the age of one and a half years with 100% matched donor. Bone marrow transplant was carried out before he developed lymphoma, but he tested positive for EBV several months before the transplant. He is doing very well and off IVIG infusions.

It is very interesting that a 3rd male sibling in family B, tested negative for the known XLP mutation but he developed Burkett's lymphoma at the age of 9 years. His immune evaluation revealed only border line IgG2 level; otherwise his immune evaluation was normal. He tested negative for the known mutation in the family. He recovered his Burkett's lymphoma. In Family B, genetic counseling did not help to decrease the recurrence of the disease and they took risk to have a diseased child hopefully to have a healthy one. They also refused prenatal diagnosis due to refusal of abortion.

Family C, one case of XLP-1

Diagnosis was made at the age of 6 months depending of the known genetic mutation as the mother is related to the mothers in family A and B from the maternal side. The child was placed on IVIG as a prophylactic measure. At the age of one and a half years, he developed small intestinal recurrent intussusceptions that required surgical exploration. During surgery, he was found to have small abdominal lymph nodes that proved to be caused by Burkett's lymphoma. He was treated by chemotherapy. No bone marrow donor was compatible with him. His EBV status was negative at the time of diagnosis of Burkett's lymphoma.

The fact that this case developed Burkett's lymphoma with no evidence of EBV infection (negative PCR) rise up the possibility of another trigger of lymph proliferation apart from EBV. We tried to prevent fulminate mononucleosis by prophylactic IVIG.

Prenatal genetic diagnosis was performed in the first pregnancy in family C. 12 fertilized ovai were tested. We found 6 diseased males and 5 carrier females and only one healthy female who were implanted. Unluckily pregnancy ended by spontaneous abortion at 12 weeks of gestation. In this case, genetic counseling did not help to decrease the incidence of the disease despite the fact that the mutation was known. Also, due to the high cost of PGD, the mother did not try it again and took the risk to have a healthy child, but did not get lucky.

We Did Not have any Mortality in these 4 new Cases

Old Cases (Now Adults) of XLP-1

I have supervised the medical care of 3 adult males from the same family who were diagnosed as XLP and survived lymphomas in their childhood. They were maintained on IVIG infusions by their hematologist since diagnosis in childhood ages. As IVIG was not available temporarily in the country, IVIG infusion was stopped. 4 months after discontinuation of IVIG infusion, one of these adult males died at the age of 35 years as a complication of severe lobar pneumonia and multi organ failure. This case proved that despite reaching the years of adulthood, some patients with XLP without bone marrow transplant are still in need of IVIG infusion.

Females who were told in the 1970s to be carriers of the disease depending on absence of EBNA were not tested for the mutation. They are now old and not interested in having children. But obviously , depending on serology is not reliable to define the carrier status of the disease. Once we isolated the mutation in this family, we depended on this mutation to define the carrier status in the female and the disease status in the male.

Discussion and Summary

We reported 4 new cases of XLP with the same mutation c.158 T (P.Thr53Ile all are related from the mother's side. Initial diagnosis was made locally in Palestine, bone marrow transplant whether as part of treatment of lymphoma (2 cases) or as prophylactic before the child develops lymphoma (one case) and chemotherapy for

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lymphoma before EBV infection (one case) were carried out in Israel, Hadassah medical center. The outcome is excellent.

Known family history of XLP helped to establish the diagnosis before isolation of the gene. 2 cases presented at the age of 1 year with recurrent otitis and spleenomegally after prolonged febrile illness. Infections were controlled by IVIG infusion, both developed lymphomas within one year (Burkett's lymphoma) to 7 years (Non Hodgkin's lymphoma) after the diagnosis. The child who had had Burkett's lymphoma developed a recurrent Burkett s lymphoma in the rectum 2 years after recovery. Both were successfully transplanted. The child who had Non Hodgkin's lymphoma was given IV Rutiximab is still on IVIG replacement despite normal in vitro functional assay, but his QIG and symptoms obligated to resume IVIG infusion. The child who had recurrent Burkett's lymphoma is doing very well after the bone marrow transplant and off IVIG infusion.

The third case was diagnosed depending on genetic mutation. Bone marrow transplant was performed before developing his first lymphoma, but after EBV infection. The procedure was performed at age of one and a half year. He is doing well, now he is 6 years old. The 4th case with the same mutation developed Burkett's lymphoma while EBV by PCR was negative. He was placed on IVIG as prophylactic measure at diagnosis. Bone marrow transplant was not carried out as no related matched donor was found. The probability of another trigger of lymph proliferation was raised up as his EBV by PCR was negative at the time of recurrent intussusceptions and lymphoma. We believe that Pre implantation genetic diagnosis (PGD) is an excellent option. Once financial issues are cleared, it will be our first choice in prevention of recurrence of this X linked inherited disease.

So far , the mortality rate of these new cases is zero% , following them for a period of 2 years the youngest and 16 years for the oldest. We encountered one mortality in an adult patient with XLP due to lobar pneumonia as IVIG infusion was discontinued. This patient did not have bone marrow transplantation as a child when he first developed lymphoma as a complication of XLP. Knowing the genetic mutation replaced all old criteria to diagnose XLP and for sure replaced the unreliable serological method.

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