# The Natural History of X-linked Lymphoproliferative Disease: Case Report of a Long-Term Survivor

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## Summary

X-linked lymphoproliferative disease (XLP1) is a rare primary immunodeficiency characterized by viral-triggered immune dysregulation and lymphoproliferation (**Fig. 1 to 3**). The classic features of XLP1 include lymphoproliferation, severe EBV infection, dysgammaglobulinemia, and lymphoma. It can also rarely manifest as gastritis, skin lesions, aplastic anemia, and vasculitis. Without hematopoietic stem cell transplant (HSCT), the mean age of survival is 7.5 years. In this case report, we present a patient with XLP1 who survived into his forties. He and his brothers originally presented to TCH in the 1980s with profound pulmonary inflammation that eluded diagnosis[2] (**Fig. 4**). Unlike his brothers, he survived life-threatening EBV infection, CNS vasculitis, and progressive respiratory decline **(Fig. 5).** On re-presentation thirty years later, we cinched his diagnosis using genetic testing and immune assays **(Fig. 6 & 7).** Unfortunately, he succumbed to lymphoma shortly afterwards **(Fig. 8).** Our patient is among the few untransplanted XLP1 patients in the literature surviving into their forties. We attribute the relative longevity of these patients to avoiding hemophagocytic lymphohistiocytosis (HLH), the most severe manifestation of XLP1.

## Background: XLP1

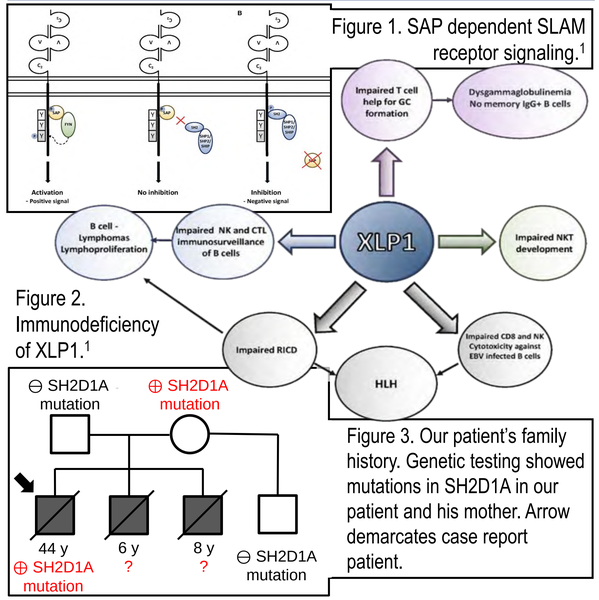


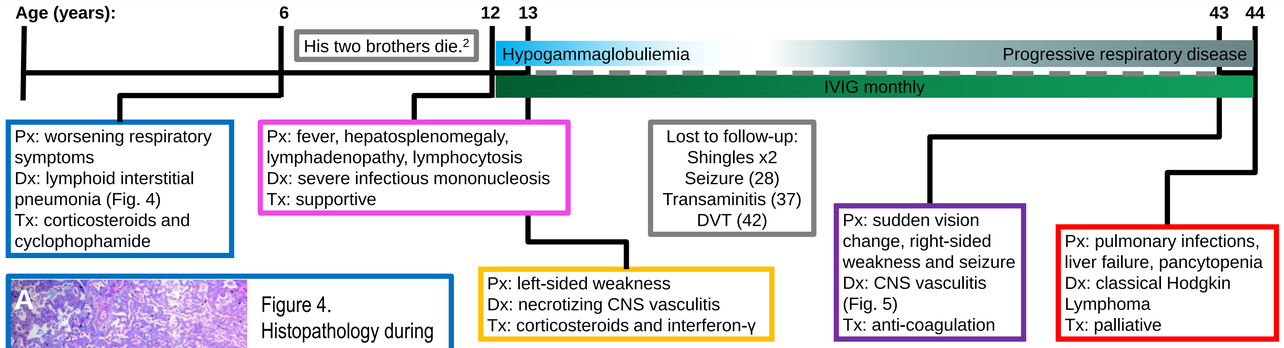

Figure 1. SAP dependent SLAM receptor signaling.[1]

Figure 2. Immunodeficiency of XLP1.[1]




Figure 3. Our patient's family history. Genetic testing showed mutations in SH2D1A in our patient and his mother. Arrow demarcates case report patient.

## Case presentation: the long-term survivor



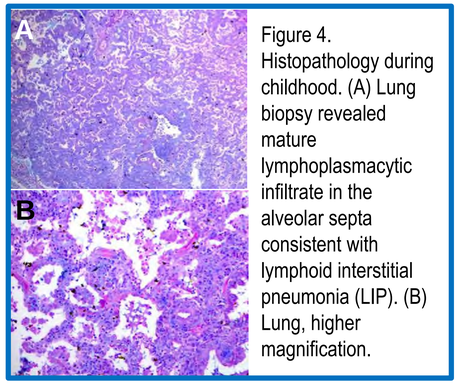




Figure 4. Histopathology during childhood. (A) Lung biopsy revealed mature lymphoplasmacytic infiltrate in the alveolar septa consistent with lymphoid interstitial pneumonia (LIP). (B) Lung, higher magnification.

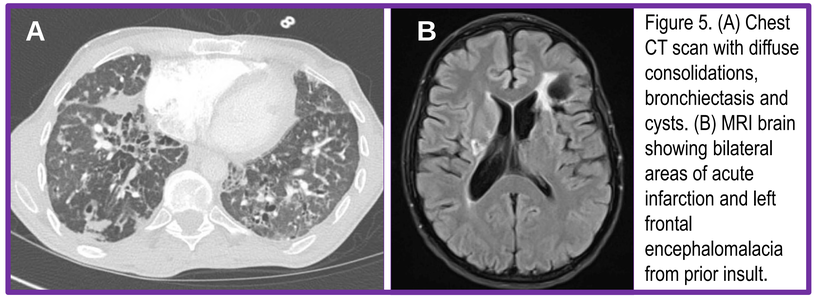



Figure 5. (A) Chest CT scan with diffuse consolidations, bronchiectasis and cysts. (B) MRI brain showing bilateral areas of acute infarction and left frontal encephalomalacia from prior insult.

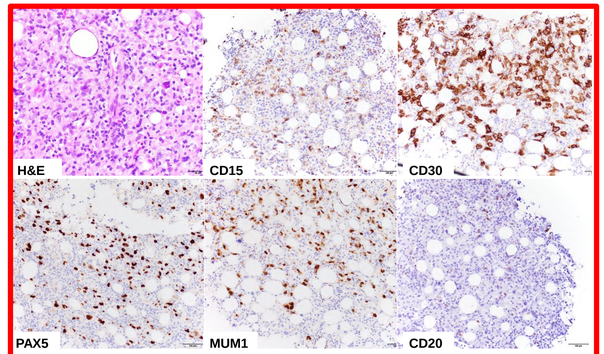



Figure 8: Bone marrow biopsy showing Hodgkin Lymphoma.

## Patient perspective

Although our patient had residual weakness and limitations in mobility, he ran a successful business from home. He also made a conscious effort and dreamed of taking his story "on the road" in order to help other people with XLP1. He passed away with this enduring wish in 2019. He is survived by his mother and his contribution to medicine.

## Immune studies: SAP deficiency

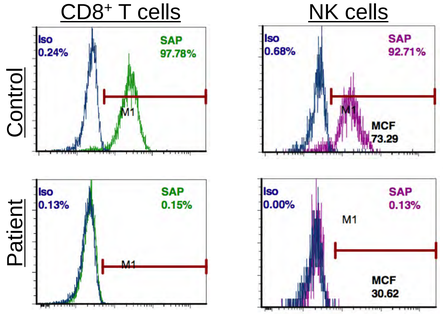



Figure 6. Flow Cytometry showing an absence of SAP staining in cytotoxic lymphocytes.

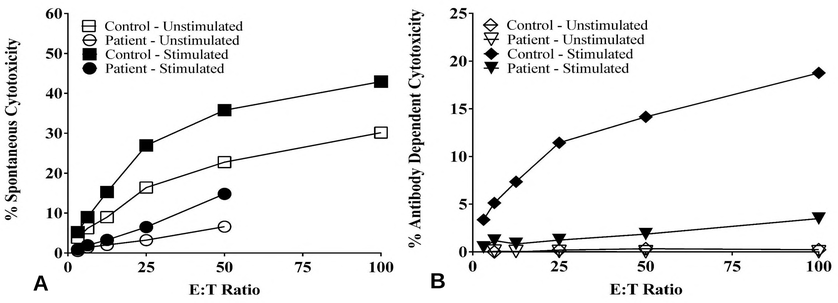



Figure 7. NK cell cytotoxicity. (A) Spontaneous cytotoxicity was measured ± IL-2 stimulation. Patient NK cells demonstrated normal spontaneous killing frequency. (B) Antibody dependent NK cell cytotoxicity was measured ± rituximab stimulation. Patient NK cells demonstrated decreased antibody dependent cell cytotoxicity.

## Conclusion

The mean age of survival for untransplanted XLP1 patients is 7.5 years with 81.3% mortality from HLH.[1] Our case represents a rare patient with untransplanted XLP1 who lived into mid-adulthood. We found only six additional cases of untransplanted XLP1 patients surviving into their forties in the literature. The shared predictor of relative longevity was that they never developed HLH. The natural history of untransplanted XLP1 patients is that they either do not survive initial childhood manifestations or succumb to complications in mid-adulthood – as exemplified by our patient and his brothers. This remains an important point to emphasize with newly diagnosed patients with XLP1 who are eligible for HSCT.

### References

1. N. Panchal, C. Booth, J. L. Cannons, and P. L. Schwartzberg, "X-linked lymphoproliferative disease type 1: A clinical and molecular perspective," *Frontiers in Immunology*, vol. 9, no. 4. Frontiers Media S.A., 04-Apr-2018.

2. B. B. Rogers *et al.*, "A familial lymphoproliferative disorder presenting with primary pulmonary manifestations," *Am. Rev. Respir. Dis.*, vol. 145, no. 1, pp. 203–208, 1992