I agree that combination of three different T cell lymphoma types (T-LBL, PTCL NOS and ALK negative ALCL) with the patient's phenotypic features, i.e. microcephaly and oligophrenia, possible Slavic origin as well as young age of lymphoma development suggest a genetic background of lymphomagenesis and possibility of NBS. However, to determine whether the patient has NBS a genetic counseling of the patient with testing for increased chromosomal breakage and NBS gene mutations (678 del5 founder mutation originally of Slavic origin account for 90% of all NBS mutations) would be helpful.
The lung lesion has areas of necrosis and scattered large LMP1+ cells, which I agree with Anna could represent a spectrum of lymphomatoid granulomatosis. Could you do, in addition to cytotoxic markers, immunostain for CD20, CD138 and immunoglobulin light chains on the lung lesion. In EBV associated LPD, EBV often induces plasma cell differentiation of infected B cells with downregulation of CD20. If feasible, could you also do ISH for EBER, which might detect much more EBV+ cells, and PCR for IgGR? I agree with Anna that lung lesion is probably not associated with paraspinal tumor, which is most likely a new event. However, EBV associated lung lesion suggests an underlying immunodeficiency. A possibility of superimposed infection can not be also entirely rule out. The patients with NBS have defective immunoglobulin genes class switching with commonly reported IgG and IgA deficiency (1). Does the patient have evidence of decreased serum immunoglobulin levels?

To answer one million dollar questions:

1. Are these malignancies clonally related?
I agree that in order to determine the clonal relationship of all T-cell lymphomas one should compare T-cell clones through the three T cell malignancies by PCR and sequencing.

2. Are only PTCL NOS and ALCL related? If yes, are they therapy related?

It seems more likely that PTCL NOS and ALCL are clonally related than all three T cell malignancies. However, to answer this question, again one should compare all three T cell clones. Whether these lymphomas are therapy related is difficult to answer. NBS, is a genetic instability syndrome predisposing to cancer development, especially lymphomas. It is possible that ALCL could evolve from the same clone as PTCL through acquisition of additional genetic alterations. Whether therapy for PTCL could contribute to clonal evolution of lymphoma is again difficult to answer given that the patient received for his PTCL only steroids. Alternatively, ALCL developed as a new entity on a background of genetic instability. It is also possible that remote chemo for T-LBL could contribute to some degree to genetic instability and lymphomagenesis later in his life, although usually therapy related malignancies are myeloid neoplasms (t-MDS/AML). It seems more likely that underlying genetic predisposition in this patient, in combination with environmental exposure to mutagenic factors, could

contribute to T-LBL and both PTCL and ALCL development. Interestingly, there is a study showing that stimulation of PB lymphocytes from patients with NBS with mitogens in the presence of IL-2 may results in spontaneous immortalization of T lymphocytes which display phenotypes typical for lymphoma cells, including phenotype of ALCL (2).

3. What is the role of assumed genetic disorder such as NBS?

Dysfunction of the maintenance of genome stability can lead to malignant transformation, genetic mutations and chromosomal instability. NBS belongs to a group of chromosomal instability disorders that include Ataxia Teleangiectasia, Bloom's syndrome, and Fanconi's anemia. The cellular hallmarks of these disorders are chromosomal rearrangements, sensitivity to ionizing radiation, and defects in cell cycle check points. NBS is rare autosomal recessive disorder characterized by genomic instability, microcephaly, growth retardation, immunodeficiency and increased cancer predisposition, in particular lymphoma and leukemia. NBS is caused by mutations in the *NBS1* gene on chromosome 8q21, which encodes Nibrin (*NBN*), a member of the hMRE11/hRAD50/hNBS1 protein complex, which is involved in the repair of DNA double strands (DSBs) by nonhomologous end-joining and homologous recombination. DSBs occurs as intermediates in physiological events such as meiotic recombination, telomerase maintenance and V(D)J recombination during early B and T cell development and immunoglobulin class switch in mature B cells but most frequently are generated by mutagenic agents such as ionizing radiation and radio-mimetic chemicals. DNA DSBs represent the most serious DNA damage, which if not repaired accurately, can result in genomic instability, including chromosome rearrangement, or gene mutations, and finally lead to cancer. Nibrin plays a key role in regulating the activity of N/M/R protein complex, which is involved in end-processing of both physiological and mutagenic DNA (3). The great majority of patients with NBS identified so far are of Slavic origin and homozygous for a 5-bp deletion in exon 6 of the NBS1 gene ("Slavic mutation"). In addition to 617del5 in exon 6 nine there are other mutation found in patients of different ethnic origin. All these mutations are located between nucleotide 657 and 1142, and are predicted to truncate the nibrin protein downstream of the N-terminal domain (4). They are believed to be hypomorphic mutations. The newly synthesized protein fragments retain the C-terminal hMRE11 interaction domain, thus partially restoring localization to the nucleus allowing the viability of NBS patients. Cancer incidence in NBS is modulated by the amount of a variant NBS protein (5) The PCR using sequence specific primers (PCR-SSP) was developed for detection of the Slavic NBS1 mutation. Also there are other PCR based rapid methods for detection of other mutations in NBS1 gene (4)

Lymphoma that develop in patients with NBS are usually B or T cell lymphomas, mostly DLBCL, B-LBL, T-LBL but also Burkitt lymphoma, T-PLL, PTCL, ALCL, cHL and EBV associated LPL cases were reported (6-8). Interestingly, the study

on 105 Polish NBS registry patients showed that 53% of patients developed cancer, mainly (>90%) lymphoid malignances (9). These NHL formed a unique morphological spectrum, predominantly DLBCL and T-LBL, with high frequency of consecutive lymphoma formation. This spectrum is different from sporadic lymphomas and lymphomas in other immunodeficient patients. Morphological and molecular analysis of consecutive lymphoproliferations revealed in six NBS patients in this study two cases of true secondary lymphoma. Furthermore, 9/13 NBS patients with lymphoma analyzed by split –signal FISH showed breaks in the Ig or TCR loci, several of which likely represented chromosomal aberrations. These combined data would fit in model in which an *NBN* gene defect results in higher frequency of DNA misrejoining of DBs breaks repair, thereby contributing to an increased likelihood of lymphoma formation in NBS patients.

Interestingly, there is also a report of a child (9-year old female) with NBS (homozygous for NBS1 657Del15) who presented with a large cell B NHL successfully treated who developed 3 years later T-cell type ALCL ALK-negative in abdominal LNs and liver with bone marrow involvement (10). The patient was successfully treated with DEX/etoposide protocol resulting in complete remission after the firs pulse. After 12 pulses etoposide was discontinued in consideration of the patient's NBS and DEX pulses continues together with weekly vinblastine. The patient has now been CCR for 24 months. (10).

In summary, several scenarios seem possible in the patient.
1 His three T-cell lymphomas are related, which could be proven by comparing T cell clone and sequencing TCR GR
2. His three T-cell lymphoma are unrelated and evolved on the background of genetic instability with predisposition to lymphoma development
3. PTCL and ALCL are related but unrelated to T-LBL
Whatever is the final combination, occurrence of three lymphoma types and possibly EBV associated LPL in the lung are unusual and strongly suggest a genetic background of lymphoma evolution in this patient with NBS as a likely common genetic denominator.

References.
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