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Occurrence of B-cell lymphomas in patients with Activated Phosphoinositide 3-Kinase δ syndrome

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To the Editor

Activated Phosphoinositide 3-Kinase δ syndrome (APDS) is a novel autosomal dominant (AD) primary immunodeficiency (PID), caused by a heterozygous gain-of-function mutation in the *PIK3CD* gene encoding the p110δ protein, the catalytic subunit of phosphoinositide 3-kinase δ (PI3Kδ)(1). The c.3061G>A mutation results in a substitution of a glutamic acid by a lysine at position 1021 (E1021K). This new PID is characterized by recurrent respiratory infections, leading to bronchiectasis, progressive lymphopenia, and defective antibody production. Both T and B cell compartments are affected as shown by the propensity of CD4+ and CD8+ T cells to die after *in vitro* stimulation and their poor capacity for cytokine production, as well as an immunoglobulin (Ig) class switch recombination defect (CSR-D). Most of the cases have an increase of serum IgM levels and a decrease of IgG2 isotype, while total IgG and IgA levels can be either normal or strongly decreased. The clinical presentation is variable, ranging from combined immunodeficiency requiring hematopoietic stem cell transplantation to an isolated primary antibody deficiency which can be well controlled by IgG substitution. In order to identify new APDS patients, we genotyped the *PIK3CD* gene at position c.3061G as described previously (1) in a cohort of 139 patients with immunological phenotype of Ig CSR-D. We found 8 new APDS patients with the E1021K heterozygous mutation in the *PIK3CD* gene (“see Tables E1 and E2”) in addition to the 17 described previously (1), bringing the total number of known patients carrying this *PIK3CD* mutation to 25. We noticed that among these eight new APDS patients two developed B-cell lymphomas, suggesting that a constitutively active PI3Kδ predisposes to malignancies. These two cases are herein reported (Table1A, 1B).

Patient 1 has no familial history of PID, but his mother died at 35 years of age of sub-arachnoid haemorrhage. He was referred to our hospital at the age of 2 years with recurrent bronchopulmonary infections, lymphadenopathy, hepato-splenomegaly, liver disease (elevated transaminases and portal septal fibrosis at liver biopsy). He had increased serum IgM levels (4.25g/L), normal IgG (5.7 g/L) and decreased IgA (0.65g/L) levels, compatible with the diagnosis of CSR-D. The CD40L and CD40 defects were excluded and intravenous IgG substitution was initiated. At 8 years of age, he developed a high grade diffuse large B-cell lymphoma (DLBCL, WHO classification) of biliary tract (Figure 1 a-c). *In situ* hybridization for Epstein Barr virus (EBV) was negative and Bcl-6 was expressed as shown by immunohistochemistry. The patient recovered after nine courses of chemotherapy (UKCCSG 9002 protocol; “see E3”). At 19 years of age, under IgG substitution, he again developed a high grade EBV(-) DLBCL of the colon, which was found to be Bcl-6 negative (Figure 1 d-f). He received CHOP (Cyclophophamide, vincristine, steroids) plus rituximab. He died from large bowel perforation and bleeding 12 days after the third course of chemotherapy.

Patient 2 belongs to a family in which two siblings were reported as suffering from a CSR-D (data from the affected sister P7 “see Tables E1 and E2”). From the age of 5 months, he

suffered recurrent upper (recurrent acute otitis media) and lower respiratory tract infections complicated by bronchiectasis, chronic non-infectious diarrhea with malabsorption syndrom and failure to thrive. Other infections were also noticed, including pericarditis caused by Echo virus infection and recurrent synovitis. The diagnosis of CSR-D was made, according to his familial history and IgG substitution was started. At 6 and 8 years of age, he displayed episodes of massive enlargement of lymph nodes (cervical and mesenteric) with no malignant feature at biopsy. Serum Ig levels revealed an increase of IgM (4.5g/L at 5 years and 13g/L at 11 years) and a decrease of IgG (<1.9g/L) and IgA (0.41 g/L). At 11 years of age, he had a new episode of cervical lymph nodes enlargement which led to the diagnosis of Hodgkin disease, histological type nodular sclerosis, stage III with localization to cervical, mediastinum, retroperitoneum and spleen (EBV status was unknown and could not be studied retrospectively) (Figure 1 g-i). Patient received chemotherapy and radiotherapy with irradiation of regions above and below diaphragma, which induced complete remission. He is now well on IgG substitution and prophylactic antibiotherapy with a follow-up of more than 10 years.

These observations extend our previous data reporting one case of marginal zone B-cell lymphoma in an adult APDS patient (1). Moreover, a recent study reports one further APDS patient who developed an EBV+ diffuse B cell lymphoma. Interestingly, authors describe a similar PID phenotype with two other gain of function mutations (E525K and N334K) in *PIK3CD* gene, including one case of EBV+ nodular sclerosis form of classical Hodgkin lymphoma (E525K) (2). Altogether these observations pinpoint to the fact that PI3Kδ hyperactivation predisposes to multiple types of B-cell lymphomas. Activation of the PI3K pathway is associated with malignant transformations and it has been shown that overexpression of p110δ can transform cells (3). Constitutive PI3K activation has been found in B-cell malignancies, e.g. Burkitt lymphomas (4, 5). Recently, somatic E1021K mutations of p110δ have been detected in diffuse large B-cell lymphomas from two patients (6) similar to our patient #1, which further supports our observation that activation of PI3Kδ signalling contributes to B cell neoplasia. We propose that a combination of defective T cell mediated immune surveillance and uncontrolled lymphoproliferation of B cells predisposes this PID to B cell lymphomagenesis. So far, only the minority of patients carrying *PIK3CD* mutation (5 out of 39, 13%) had been diagnosed with lymphomas. However, the risk of malignancies is likely to increase with age, modified by additional acquired somatic mutations. Most APDS patients currently receive treatment with antibiotics and IgG replacement. Such treatment reduces infections, but is unlikely to prevent lymphomas. We have found that selective p110δ inhibitors IC87114 and GS-1101 (CAL-101 or Idelalisib) reduce activity of the mutant p110δ *in vitro* and in cells of APDS patients *ex vivo* (1). GS-1101 has been in clinical trials for treatment of chronic lymphocytic leukemia (CLL) and early data suggest that the drug is well tolerated for extended periods of exposure (7). Therefore, GS-1101 and other selective p110δ inhibitors may provide a novel specific therapy for APDS patients that prevent lymphoma development. Susceptibility to lymphomas is observed in other well defined PID, such as the AD hyper-IgE syndrome due to heterozygous mutations in *STAT3* and in autosomal recessive *IL10RA* or *IL10RB*-deficiencies, suggesting a role for the IL-10R/STAT3 pathway in controlling lymphomagenesis (8). Patients with common variable immunodeficiency are also prone to

develop lymphomas (9). Physicians should be aware of this complication that strongly worsens the prognosis for PID patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AD	autosomal dominant
PID	primary immunodeficiency
Ig	immunoglobulin
CSR	class switch recombination
CSR-D	class switch recombination deficiency
DLBCL	diffuse large B-cell lymphoma
EBV	Epstein Barr virus

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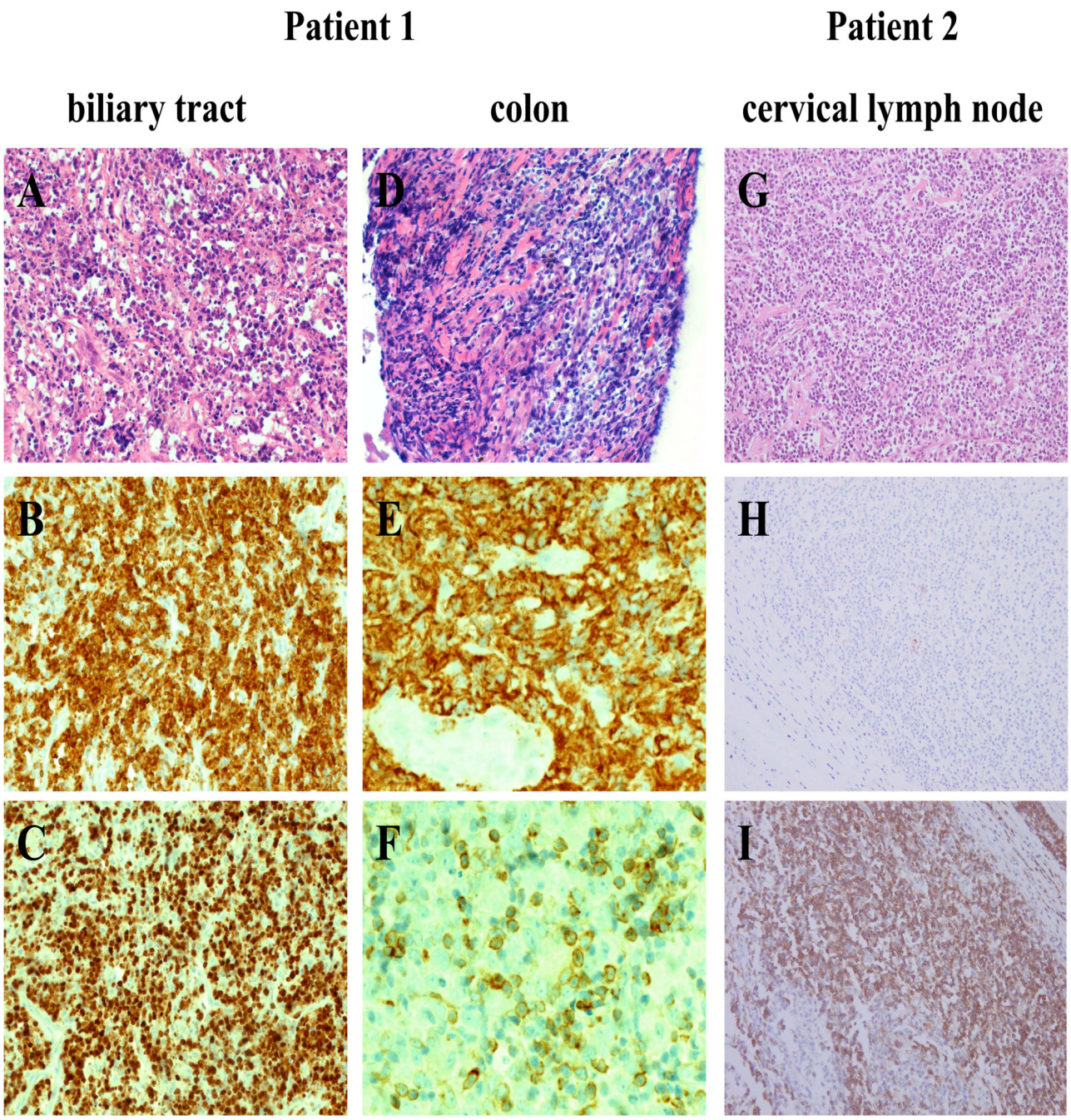

Figure 1.
B-cell lymphomas.

Histological staining of patient 1: (A) H&E (200×); (B) CD79a and (C) Ki67 staining of DLBCL of the biliary tract. (D) H&E (200×); (E) CD20 and (F) Bcl-2 staining of DLBCL of the colon. Histological staining of patient 2 showing view atypical large cells: (G) H&E (200×); (H) CD30 and (I) CD3 staining of Hodgkin lymphoma of a cervical lymph node.

Table 1A

patients	**P1**	**P2**
Year of birth	1986	1990
Age of onset	2 yrs	5 months
Main clinical features	Recurrent LRT infections, liver damage, HMG, SMG, lymphadenopathy	Recurrent LRT infections bronchiectasis , chronic diarrhea, failure to thrive HMG, SMG
Cytopenia		Neutropenia
Main biological features	Lymphopenia	Lymphopenia
age	2 yrs	5 yrs
IgM g/l (N)	4.25 (0.58-1.53)	4.5 (0.54-1.55)
IgG g/l (N)	5.7 (3.35-8.96)	<1.9 (5.49-11.54)
IgAg/l (N)	0.65 (0.27-1.22)	0.82 (0.41-1.57)
subclasses g/l		
IgG1 (N)	3.71 (>3)	
IgG2 (N)	1.5 (>0.30)	
IgG3 (N)	0.64 (>0.12)	
IgG4 (N)	0.3 (>0.04)	
Malignancies	High grade DLBCL of biliary tract (EBV−, Bcl–6+; age 8yrs); High grade DLBCL of the colon (EBV−, Bcl-6−; stage IVB; age 19yrs)	Hodgkin lymphoma stage III
treatment	IVIg from 3yrs on Chemotherapy, rituximab	IVIg from 7 yrs on Chemotherapy, radiotherapy (11 yrs)
outcome	Died from large bowel perforation and bleeding post chemotherapy	In remission, alive

Footnote : LRT : low respiratory tract infections, HMG: hepatomegaly, SMG: Splenomegaly, yrs: years, N: normal values for age, DLBCL: diffuse large B-cell lymphoma, WHO classification, IVIgG: intravenous Immunoglobulins, SCIgG: subcutaneous IgG

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Table 1B

Lymphocyte populations

Patients	P1	P2
Age at analysis (yrs)	18	11
Number of lymphocytes (µl)	790*	1190*
CD19+ (µl)	104*	3*
CD3+CD4+ (µl)	245*	369*
CD3+CD8+ (µl)	349	584
CD16+CD56+ (µl)	55*	119

* value < normal (see E4)