



Chronic granulomas of the skin triggered by rubella virus in a patient with ASXL1 mutation

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Introduction: ASXL1 somatic mutations have been implicated in patients with myelodysplastic syndrome, acute myeloid leukemia, and acquired aplastic anemia. Mutations in other regions of the gene have been implicated in patients with severe developmental issues and malformation disorders. We report here a patient with chronic granulomatous skin lesions, learning difficulties, and mild myelodysplasia with an ASXL1 mutation.

Case Presentation: An 11-year old female of Taiwanese, Scottish and Norwegian descent with a history of learning difficulties, blood dyscrasia, and hypocellular bone marrow was referred to Immunology at 3 years of age with a history of chronic granulomas of the skin. She initially presented at 3 years of age with erythematous macules on the left leg and right arm which progressed to crusted and ulcerated plaques. She was treated with multiple courses of oral antibiotics as well as topical antimicrobial and antifungal therapy. She was immediately referred to Dermatology and underwent multiple punch biopsies which revealed non-specific necrotizing granulomas with ulceration. She was subsequently referred to Immunology for consideration of underlying primary immunodeficiency (PID). Microbiology studies performed on a full skin biopsy of the granulomatous lesion in 2016 were negative for polymerase chain reaction (PCR) of mycobacterial species, and bacterial and fungal cultures. The patient was referred to Hematology/Oncology for persistent macrocytosis (range 94 to 98 fL) unresponsive to folate and vitamin B12 supplementation. As a result of the treatment failure of supplementation, bone marrow biopsies were performed in 2012 and repeated in

2016. Results revealed findings suggestive of a possible myelodysplastic syndrome or an early bone marrow failure syndrome.

Further infectious history revealed 2 episodes of bacterial pneumonia, recurrent acute otitis media, and 1 episode of Epstein-Barr virus (EBV) infection. Most recently, she developed viral warts on her right middle finger and feet at 10 years of age. The patient was born at term with no significant complications in the neonatal period. There was no history of consanguinity. Family history was significant for rheumatoid arthritis in the mother. All routine childhood immunizations, including live viral vaccines, were administered and tolerated. Physical examination was positive for subtle dysmorphic features. Her weight and height consistently fell between the 3rd to 15th percentiles. However, her head circumference fell between the 50th to 75th percentiles. The skin exam was significant for chronic granulomatous lesions with several ulcerated lesions located on the skin overlying the right upper arm, knees bilaterally, and left anterior thigh and popliteal fossa. Residual atrophic scarring at previous sites of granulomas were present. Examination of the abdomen revealed no evidence of hepatosplenomegaly.

Investigations: The 1, 2, 3 Dihydrorhodamine assay was normal at 3 years of age which ruled out chronic granulomatous disease. A sweat chloride test was negative. CBC was normal including normal lymphocyte and neutrophil counts. She had persistent macrocytosis but no anemia. Immunoglobulin levels including IgG, IgA, IgM, IgE were normal at 4 years of age. Lymphocyte immunophenotyping results at age 4 years

are as follows ($\times 10^9$ cells/L): low CD3 of 0.26 (0.9–4.5), low CD4 of 0.17 (0.5–2.4), and low CD8 of 0.07 (0.3–1.6). B lymphocyte counts and NK cells were normal. Vaccine titres to diphtheria and pertussis were normal at 4 years of age, however she had a very high rubella titer of >500 IU/mL. Low quantitative immunoglobulins were noted with an IgG of 3.85 g/L (6.20–19.10 g/L) starting at age 6, low IgA of 0.24 g/L (0.3–2.9 g/L) at age 8 and a normal IgM of 0.61 g/L (0.31–1.80 g/L). Urine and blood PCR for rubella virus was negative. Rubella virus was isolated in a skin biopsy suggesting underlying etiology of her chronic skin lesions. Genetic testing including microarray and testing for Fanconi anemia were normal. Cytogenetics revealed a normal karyotype. FISH was normal for 22q11.2 deletion. Whole exome sequencing (WES) revealed that she is a compound heterozygote for ASXL1 mutation with both parents demonstrated to each be carriers of a different point mutation in the same gene. The patient is currently followed by Immunology, Hematology/Oncology, Dermatology and Medical Genetics for ongoing management.

Discussion: Granulomas may develop in response to a local antigenic trigger leading to activation of macrophages and T-lymphocytes. Chronic granulomas have been reported in pediatric patients with PID such as T-cell immunodeficiency, and in patients with ataxia telangiectasia (AT). AT is caused by a loss of function mutation in the ATM gene on chromosome 11q22 which encodes a protein kinase involved in repair of double stranded DNA breaks. In case reports of patients with AT, prolonged antibiotic treatment for chronic granulomas showed no clinical improvement, and repeated microbial cultures of the lesions and PCR for viruses were negative. Further testing of granulomatous lesions with high throughput sequencing (HTS) detected sequences of rubella virus vaccine. These results indicate that the rubella virus may persist on the skin of individuals with PID. Rubella virus has also been isolated in patients with recombinant-activating gene (RAG) deficiencies.

There are currently no antiviral drugs approved to treat chronic rubella infections. Nitazoxanide (NTZ) has been approved by the Food and Drug Administration for treatment of enteritis secondary to parasites, protozoa, and anaerobic bacteria. It also has broad-spectrum antiviral activities by targeting host functions that are involved in viral replication. A case report of a patient with B-cell and T-cell dysfunction revealed rubella virus (RV) in the epidermis via

immunofluorescence staining of a skin biopsy. The patient was treated with 500 mg of NTZ twice daily for 2 months. Repeat immunostaining of skin biopsies taken from the same lesion revealed almost complete elimination of rubella virus antigen from the lesions. The treatment did not, however, result in noticeable clinical improvement of the granuloma despite elimination of the antigen. Further studies on the inhibitory effects of NTZ on RV infection revealed inhibition of production and reduction in the number of RV-positive cells in the NTZ-treated cultures in comparison to controls. NTZ can inhibit replication of different RV strains which have been isolated in patients including RA27/3 vaccine strain. Furthermore, studies on the effect of NTZ on viral replication was observed when the treatment was initiated in the early stage of the replication cycle. Anti-viral mechanisms of NTZ are poorly understood however, it appears to act broadly on cellular pathways involved with RNA synthesis as opposed to specific viral antigens. Based on these findings, NTZ may be effective in preventing spread of the RV which could prevent formation of granulomatous lesions in new locations on the body of infected patients.

Conclusion: Based on the literature describing persistence of RV strains in patients with features of PID and evidence to suggest that treatment with NTZ can eliminate the RV antigen and inhibit replication of the virus, it is important to consider more robust testing such as HTS earlier in the diagnostic work up of patients with chronic granulomas of the skin resistant to treatment. Although NTZ was successful in eliminating the virus in skin biopsies of affected patients, clinically, the granulomas persisted. If the virus is detected earlier in the clinical course via specific testing for RV strains, it is possible to initiate treatment early to prevent long-term atrophic scarring.

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Novel heterozygous PIK3CD mutation presenting with only laboratory markers of combined immunodeficiency

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Introduction: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Delta (PIK3CD) is a heterodimer of p110δ and p85 subunits, found primarily in leukocytes. It generates phosphatidyl-inositol

3,4,5-trisphosphate (PIP3), a key recruiter of PH domain-containing proteins, including AKT1 and PDKP1, which are the initiators for activating signalling cascades. It is involved in mediating cell growth,

survival, proliferation, motility, morphology; in lymphocytes including T-, B- and NK-cells. Recently an increasing number of patients have been described with heterozygous PIK3CD gain of function mutation, leading to a combined immunodeficiency with both B- and T-cell dysfunction. They suffer recurrent respiratory infections, often associated with bronchiectasis and ear and sinus damage, as well as severe recurrent or persistent infections by herpes viruses, including EBV induced lymphoproliferation.

Patient Description: We describe here 2 patients—mother and daughter—with heterozygous PIK3CD mutation, both diagnosed following an abnormal newborn screen for severe combined immunodeficiency (SCID) in the child.

Patient 1: A currently 3.5 years old female patient, presented with initial abnormal newborn screen for SCID and T cell lymphopenia. She has had no recurrent infections and had not needed antibiotic therapy, no warts, or fungal infection of nails or thrush. Her initial TREC results on newborn screen was low, 11.3 copy/3 μ L. Whole blood TREC 588, which is below the normal. Her laboratory results were remarkable for intermittent leukopenia, attributed to lymphopenia and neutropenia. Lymphocyte immunophenotyping showed low total CD3+, CD4+, and CD8+ levels, normal Nk, and CD19+ B cell counts. Her CD45RA/RO of CD4+ cells demonstrated low number of naiveCD4 cells. In vitro responses to PHA were depressed initially, but gradually increased.

Patient 2: Mother of patient 1, had been evaluated due to the laboratory findings in her daughter and was found to have an individual heterozygous mutation in the gene PIK3CD. She has had a history of eczema and otitis during childhood. Her laboratory work up showed normal complete blood count, normal differential and normal lymphocyte immunophenotyping. However her CD45RA/RO of CD3+ and CD4+ cells demonstrated a lower number of naive cells, and elevated memory population compared to control, similar to her daughter. She also had reduced in vitro responses to PHA as well as low in vitro T cell responses to stimulation with specific antigens.

Signalling evaluation were done on both on peripheral blood lymphocytes as well on flow cytometry assisted selected T-cells (Surface phenotypes were determined by flow cytometry analysis on a Coulter EPICS V Flow Cytometer from Beckman Coulter (Brea, Calif)), following ficoll separation. Both patient's and control cells were selected, and either left un-stimulated or were

stimulated with anti-CD3 UCHT1 antibody (5 μ g for 4×10^6 cells), and incubated for 10 minutes on 37 °C. Following this 1%Triton-X100 lysis buffer was used for cell lysis. Whole-cell lysates were analyzed by Western blotting. All blots were repeated at least twice. The antibodies used for Western blotting were: Anti-pAKT Ser473(Invitrogen), anti- G α (i) (CellSignaling). The signalling test shows a clear increase in the baseline phosphorylation in patient 1.'s T-cells, as well as both patients show hyperactivation of the catalytic domain in different levels, resulting in increased phosphorylation of AKT on activation.

Discussion: Gain of function mutations affecting the PIK3CD gene, encoding the catalytic subunit of phosphoinositide 3-kinase, were described in the past few years, as an autosomal dominant disease associated with lymphadenopathy, autoimmune cytopenias, splenomegaly, susceptibility to EBV, CMV as well as HSV infection, and an increased risk for lymphoproliferation leading to Activated PIK3-delta syndrome (APDS). The clinical course of APDS is highly variable, ranging from combined immunodeficiency, with recurrent infections, autoimmune complications, requiring stem cell transplantation, through isolated antibody deficiency, to asymptomatic adults.

The presentation of the patient described here is unique, as no other case with gain of function (GOF) PIK3CD defect had been detected by newborn screen (NBS) for SCID (severe combined immunodeficiency). Surprisingly the clinical course so far had been unremarkable. Further, the mother appears to be completely asymptomatic inspite of having an identical mutation to her daughter.

Nevertheless, the persistent lymphopenia in the proband, of clear GOF origin as demonstrated by AKT phosphorylation, indicate PIK3CD dysfunction. Because of the wide gap between laboratory findings and clinical manifestations, this kindred poses both a diagnostic as well as a of treatment challenge.

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A case of *KAT6A* mutation associated with immunodeficiency and granulomatous lymphocytic interstitial lung disease

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Background: The *KAT6A* gene encodes a lysine acetyl transferase which is involved in histone acetylation. It is implicated in the regulation of gene transcription and expression. *KAT6A* is thought to be required for development of the hematopoietic system and thymic tissue, consistent with the observation that *KAT6A* knockout mice are neutropenic (Katsumoto et al. 2006; Sheikh et al. 2017). In the clinical setting, *KAT6A* mutation has been associated with a syndrome of intellectual disability, hypotonia, feeding difficulties, cardiac defects, craniosynostosis, and distinct facial dysmorphisms. Here we present the case of a boy with *KAT6A* deficiency who had additional immunological features not previously reported in patients with *KAT6A* mutations. These features included recurrent infections, hypogammaglobulinemia, splenomegaly and pancytopenia. Moreover, he developed granulomatous lymphocytic interstitial lung disease (GLILD), a condition commonly seen in patients with common variable immunodeficiency (CVID).

Case Presentation: The patient was referred to the Pediatric Immunology Clinic at the age of 11 years, following hospitalization with *Streptococcus pneumoniae* bacteremia and pneumonia. A chest X-ray done at the time of admission showed multifocal infiltrates. A blood culture identified *S. pneumoniae* bacteremia and the patient was treated with appropriate IV antibiotics. Serum IgG at that time was undetectable (<0.5 g/L). The patient had a history of 1 previous admission for pneumonia in which multifocal infiltrates were identified on his Chest X-Ray, and for which he was treated with levofloxacin. He furthermore had a 6-year history of clinically diagnosed pneumonias that occurred approximately once a year and were treated with oral antibiotics in the community. He did not have any history of sinus, ear, or skin infections, nor had he had any other episodes of bacteremia, meningitis, abscesses,

dental infections, or osteomyelitis. He had not had fungal or viral infections. He also had a history of splenomegaly and fluctuating mild-to-moderate pancytopenia, followed by Hematology with no specific diagnosis. He had not required any transfusions.

The patient was born via emergency Caesarian section for possible placental abruption and the presence of meconium at 38 + 5 weeks. APGAR scores were 2, 6, and 8 at 1, 5, and 10 minutes respectively and he required positive pressure ventilation and CPAP. MRI at the time was normal but his intellectual delay would later be clinically attributed to Hypoxic Ischemic Encephalopathy. He was noted to have a broad nasal bridge, strabismus, micrognathia, low set ears, a high arch palate and club feet. Initial Genetic and Metabolic workup did not ascertain a diagnosis. Parents are not consanguineous. There is no family history of Immune Deficiency or recurrent infections, or of syndromic features or developmental delay.

Laboratory Evaluation: Upon initial evaluation in the clinic, CBC showed a leukocyte count of 3.6, hemoglobin 113 and platelets 125. Lymphocytes were 1.4 with neutrophils of 2.0. Repeat IgG was 0.34 g/L, IgA <0.07 g/L and IgM 0.41 g/L. Lymphocyte immunophenotyping demonstrated normal T cell counts, but profoundly low B cells with 40×10^6 cells present (lower limit of normal 270×10^6). Measles, mumps, rubella, and varicella serology were negative despite timely immunization. Neutrophil oxidative burst index testing was normal.

Clinical Evolution: Following the initial consult, he was started on IVIG replacement therapy. Genetic evaluation for X-linked agammaglobulinemia was negative. The patient subsequently presented to hospital with fever and cough and was admitted for treatment of his respiratory infection. He underwent a chest CT scan which showed diffuse pulmonary nodules, mild

interstitial thickening and extensive lymphadenopathy. An echocardiogram was done which demonstrated pulmonary hypertension with RVSP 63 mm Hg and RAP 92 mm Hg. Bronchoscopy was unremarkable and bronchoalveolar lavage was negative for infection or malignancy. A bone marrow aspirate showed no evidence of malignant infiltration. A lymph node biopsy was negative for malignancy. Serum and BAL PCR testing for CMV, EBC, HHV6, and HIV were all negative. Fungal cultures, mycobacteria, legionella, and nocardia were also negative. A lung biopsy specimen showed lympho-histiocytic infiltrate and peribronchial chronic inflammation with non-caseating sarcoid-like granulomas. Also seen were Langerhans giant cells with Schaumann bodies, consistent with granulomatous lymphocytic interstitial lung disease (GLILD). The lung disease was thought to be secondary to his immune deficiency. Treatment was initiated with systemic oral steroids, which greatly alleviated his respiratory symptoms.

Chromosomal microarray was sent and did not reveal a diagnosis. Whole exome sequencing (GeneDX Laboratories) revealed a *de novo* pathogenic heterozygous variant in the *KAT6A* gene, p.R1024X.

Discussion: The *KAT6A* gene encodes a lysine acetyl transferase, which is involved in histone acetylation and regulates gene transcription and expression. It is also known as *MOZ* or *MYST3* and is located on chromosome 8p11. Mutations in *KAT6A* were initially implicated as the cause of recurrent translocations in patients with acute myelogenous leukemia (Tham et al. 2015; Millan et al. 2016). Case reports have identified common dysmorphic and developmental features with autosomal dominant *de novo* mutations in *KAT6A*, which are similar to our case. Features include hypotonia at birth, difficult delivery with low Apgar scores requiring resuscitation, global developmental delay, feeding difficulties, strabismus, micrognathia and broad nasal bridge (Arboleda et al. 2015; Tham et al. 2015). A significant delay in speech has been consistently seen in other reported cases (Tham et al. 2015; Millan et al. 2016).

While this case is morphologically and developmentally in keeping with previously described *KAT6A* mutations, the finding of profound B-lymphopenia and hypogammaglobulinemia is to our knowledge a unique presentation. It is unclear to what extent the protein is involved in immunodeficiency. In rodent studies, *KAT6A* was found to be required for thymus development and the hematopoietic system

(Katsumoto et al. 2006; Sheikh et al. 2017). Impaired B cell differentiation was found in knockout mice (Good-Jacobson et al. 2014). These findings are consistent with our case of hypogammaglobulinemia. Recently, a study showed that cyclic neutropenia may also be seen in patients with *KAT6A* mutation and perhaps an under-diagnosed feature (Gauthier-Vasserot et al. 2017). Although Immune Deficiency has not been reported with this diagnosis, recurrent infections have been reported in a few cases (Arboleda et al. 2015; Millan et al. 2016).

To our knowledge, this is also the first case of a patient with *KAT6A* mutation with confirmed GLILD. There have been 2 reported cases where phenotypic features of a *KAT6A* mutation had chronic lung disease, but not specifically granulomatous disease. GLILD is a well-known complication of Common Variable Immune Deficiency, in which hypogammaglobulinemia is the central feature (Park and Levinson 2010). This would suggest that the immune features in this case may have contributed to the patient's development of GLILD.

Conclusion: Here we report a case of a patient with a novel *KAT6A* mutation, presenting with dysmorphisms and developmental abnormalities typical for this disorder, as well as pancytopenia, profound B-lymphopenia, hypogammaglobulinemia, and granulomatous lymphocytic interstitial lung disease (GLILD). We postulate that this mutation may be responsible for our patient's immune deficiency as well as his lung inflammation. We propose that patients with *KAT6A* mutation be screened for such issues with immunoglobulin quantification, lymphocyte immunophenotyping, and, if an immune defect is detected, surveillance lung imaging. This would allow for early intervention with IVIG replacement which may prevent or delay progression to interstitial lung disease.

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Two cases of somatic p.G13C mutation in *KRAS* causing RAS-associated autoimmune lymphoproliferative disease (RALD)

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Introduction: RAS signaling proteins are small, regulatory guanosine triphosphatases (GTPases) that play a critical role in signal transduction and cell proliferation, differentiation, and apoptosis (Aoki et al. 2008; Calvo et al. 2015; Ragotte et al. 2017). The RAS family of proteins consists of Harvey-RAS (HRAS), Kirsten-RAS (KRAS) and neuroblastoma RAS (NRAS) (Aoki et al. 2013). Germline RAS mutations have been associated with specific autosomal dominant developmental

disorders, known as “RASopathies”, including Costello (HRAS), Noonan (PTPN11, KRAS, and SOS1) and cardio-facio-cutaneous syndromes (KRAS, BRAF, MEK1, and MEK2) (Aoki et al. 2008; Niemela et al. 2011; Takagi et al. 2011; Ragotte et al. 2017). These syndromes carry an increased risk of autoimmunity and malignancy (Calvo et al. 2015). Somatic gain-of-function (GOF) mutations in RAS genes are found in >30% of all human cancers (Niemela et al. 2011).

There have been several reports of somatic GOF mutations in the *KRAS* and *NRAS* genes associated with a non-malignant syndrome of autoimmunity and dysregulation of leukocyte homeostasis (Niemela et al. 2011; Ragotte et al. 2017). This syndrome has now been defined as RAS-associated autoimmune lymphoproliferative disease (RALD). RALD typically presents with autoimmunity, lymphadenopathy, splenomegaly, cytopenias, and monocytosis (Ragotte et al. 2017). This presentation can appear similar to autoimmune lymphoproliferative syndrome (ALPS), however, unlike ALPS, patients with RALD lack the characteristic peripherally expanded CD4-/CD8- 'double-negative' T-lymphocytes, do not have a defect in the FAS pathway of apoptosis, and lack the biomarkers typically associated with ALPS (IL-10 and sFASL) (Niemela et al. 2011; Ragotte et al. 2017).

We describe 2 cases of RALD caused by somatic p.G13C mutations in the *KRAS* gene, each presenting with a distinct phenotype, the first of which has been recently published (Ragotte et al. 2017).

Patient 1: A non-dysmorphic Canadian First Nations boy, who was the product of a dichorionic-diamniotic twin pregnancy first presented to the healthcare system at age 4 years with massive cervical lymphadenopathy causing superior vena cava obstruction. An excisional biopsy of a lymph node revealed a marked histiocytic (CD68+, S100+) infiltrate, considered to be in keeping with Rosai-Dorfman disease. He was treated with prednisone, methotrexate and mercaptopurine, however, the lymphadenopathy persisted. Following treatment, he developed pancytopenia and hepatosplenomegaly. A bone marrow biopsy revealed non-specific reactive changes, with no evidence of myelodysplasia, malignancy or hemophagocytosis.

At age 7 years, he presented with a pericardial effusion and cardiac tamponade. Pericardiocentesis revealed serosanguinous fluid with predominant polymorphonuclear cells and lupus erythematosus (LE) cells. Investigations showed antinuclear antibody (ANA) elevated at 1:1280, and positive anti-double stranded DNA (anti-ds-DNA) meeting the clinical diagnostic criteria for SLE. He later developed non-erosive and non-deforming inflammatory arthritis of his wrists, knees, ankles, and fingers. There was a positive family history of autoimmunity with SLE in the maternal aunt and rheumatoid arthritis (RA) in the maternal grandmother.

Immune studies showed hypergammaglobulinemia with IgG 20.7–25 g/L (normal, 5–14.6 g/L), with normal IgA 0.76 g/L (normal 0.4–2.4 g/L), and IgM 0.38 g/L (0.15–1.88 g/L), and no increase in CD4-CD8- double negative T cells, inconsistent with ALPS.

Because of the rare combination of Rosai-Dorfman syndrome and SLE, and unusually severe disease course, whole exome sequencing (WES) was conducted and revealed a mutation in the *KRAS* gene (c.37G>T; p.Gly13Cys). This mutation was unique to the patient, and not present in either parent. Sanger sequencing of the patient's saliva-derived DNA showed a lower peak for the *KRAS* c. 37G>T mutation compared to the whole blood-derived DNA, consistent with somatic mosaicism.

His treatment course over the years has consisted of pulse high-dose corticosteroids, rituximab, intravenous cyclophosphamide and azathioprine. Most recently, his disease has been relatively well controlled on mycophenolate mofetil (MMF), although he continues to have stable mild pancytopenia, hepatosplenomegaly and intermittent arthritis. His growth has also been very restricted, which was thought to be secondary to his underlying condition, in addition to chronic corticosteroid use.

Patient 2: This non-dysmorphic, previously well, Caucasian girl first presented at age 5 years with thrombocytopenia, lymphopenia, neutropenia and monocytosis, with marked splenomegaly. A bone marrow biopsy was judged to be normal with no evidence of malignancy or myelodysplasia.

Immunologic workup revealed hypergammaglobulinemia with IgG 22.4 g/L (normal 5.1–13.6 g/L), IgA 3.03 g/L (normal 0.25–1.9 g/L), and IgM 2.10 g/L (normal 0.31–2.08 g/L). Flow cytometry showed a uniform decrease in T and B cell numbers with normal NK cell numbers. There was no increase in CD4-CD8-T cells, ruling out ALPS. Vaccine titres showed positive diphtheria (1.94IU/mL) and tetanus (4.45IU/mL) anti-toxins. WES revealed a pathogenic variant in the *KRAS* gene (c.37G>T; p.Gly13Cys) in the patient, but neither parent. Experiments to formally establish the suspected somatic nature of this mutation are ongoing.

Discussion: We present 2 unusual cases of somatic p.G13C mutations in the *KRAS* gene. This amino acid position is located within the p-loop of the *KRAS* protein, where it plays an active role in GTP-hydrolysis (Lu et al. 2016). It is hypothesized that the substitution

of glycine with a larger amino acid such as cysteine diminishes KRAS GTPase activity, leading to a GOF phenotype, driving cellular proliferation and inhibiting T-cell apoptosis (Niemela et al. 2011). KRAS mutations in this position have been reported in malignancy, RALD and Noonan syndrome (Ragotte et al. 2017). Neither patient had the clinical features of Noonan syndromes, nor evidence of malignancy, making RALD the most appropriate unifying diagnosis.

Calvo et al. (2015) presented 13 patients with RALD, all of whom presented with cytopenias, hypergammaglobulinemia, splenomegaly, B-cell lymphocytosis and persistent relative or absolute monocytosis. Two of this cohort were found to have the same pG13C KRAS mutation.

Niemela et al. (2011) also reported the case of a Caucasian female who presented at 4 years of age with splenomegaly, autoimmune hemolytic anemia and thrombocytopenia, with polyclonal hypergammaglobulinemia and positive serology for several autoantibodies, who was also felt to have RALD.

Both of our patients similarly presented with cytopenias, splenomegaly, hypergammaglobulinemia and monocytosis. Patient 1 had the additional complexity of meeting diagnostic criteria for both Rosai-Dorfman syndrome and SLE, and is the first reported RALD case showing histiocytosis.

Although there is currently no specific molecularly-targeted treatment for RALD, research is currently underway to develop both broad-spectrum KRAS inhibitors and inhibitors that target the specific KRAS mutations found in malignancy, both of which have potential applications in patients with RALD (Ragotte et al. 2017).

Conclusions: RALD should be considered on the differential diagnosis of patients presenting with autoimmune disease, cytopenias, lymphoid organ expansion and monocytosis. In addition, RALD should be considered in cases where patients are suspected to have ALPS, but are lacking the characteristic 'double negative' T cell expansion.

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Chronic mucocutaneous candidiasis (CMCC): a patient presenting with a novel mutation in the IL-17 receptor alpha

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Keywords: CMCC, IL-17RA

Background: Chronic mucocutaneous candidiasis (CMCC) has traditionally encompassed endocrinopathy, autoimmunity and infection of the skin, nails, oral and genital mucosa typically caused by *C. albicans*; an organism that is found to be commensal in healthy individuals. Most cases thus far were found to have mutations in AIRE or STAT1. In recent years, chronic candida infections which may be a common feature in multiple profound T cell deficiency, can also be identified in a rare group of more selective immune defects. IL-17RA is an example of such a defect which is inherited in an autosomal recessive fashion.

There have been so far a number IL-17RA deficiency reports proposing the association of *S. aureus* skin infections and various degrees of candidiasis. Functionally, IL-17RA is expressed on neutrophils and is activated via the binding of the cytokine IL-17 which appears to contribute to cutaneous immunity to *C. albicans* and *S. aureus* infections. This cytokine is secreted from Th17 cells that are activated in the presence of microbial antigens including *C. albicans* and result in the recruitment of neutrophils to the site of infection (Nahum 2017). Mutations within the IL-17RA could alter effective clearance of these infections thus possibly underlying the phenotype. Most of the mutations reported were homozygous with premature stop codons upstream from the transmembrane domain (Levy et al. 2016). Functionally, these prevent expression of the receptor on the circulating leukocytes.

Methods: We report of patient presenting with the phenotype of chronic candidiasis associated with a deleterious mutation in IL-17 alpha receptor.

Results: Our patient is a 10 year old male, born at term to non-consanguineous parents. The mother is healthy but the father has been diagnosed with Crohn's disease as well as having cutaneous fungal

infections with tinea versicolor. The patient presented originally with a history of eczema at the age of 9 months complicated with recurrent superinfection with community acquired methicillin-resistant *S. Aureus*. Other infections in the first few years of life included 1 episode of pneumonia and acute otitis media. He had recurrent oral thrush and diaper rash within the first year of life that did not respond to topical Nystatin. He has till present day, continued on antifungal prophylaxis with Fluconazole and topical Terbinafine, and the thrush and diaper rash had improved. In childhood he had recurrent mouth lesions that were consistent with impetigo and responded well to topical Fucidin. He was also diagnosed with asthma, but had no evidence of endocrinopathy, or other autoimmunity manifestations. Evaluation of the immune system most recently showed a normal IgG level of 8.4 g/L, IgA of 0.8 g/L, and IgM 0.6 g/L. Lymphocyte markers demonstrated normal numbers of CD19(295), CD3 (1361), CD4 (818), and CD8(402) positive cells and NK cells at 160. Specific antibody levels were protective to Rubella, Varicella and Tetanus and a good response to Pneumococcal vaccine. Proliferative responses to phytohemagglutinin were normal.

Genetic testing for STAT1 and AIRE genes were both normal.

Conclusion: We report a child presenting with recurrent *S. aureus* skin infections, atopy and limited oral thrush and diaper rash. He was initially thought to have an AD mutation such as STAT1 given the father's history of autoimmunity. However, mutations of STAT1 and AIRE were negative but whole exome genome sequencing revealed a novel IL17RA mutation. Clinically, this case appears interesting because he presented a diagnostic challenge. While he did have chronic oral thrush and a diaper rash, he also had eczema, skin staph infections and other oral lesions.

Because both *S. Aureus* and *Candida* are organisms found to be commensal in healthy individuals, these infections can occur after insults to skin such as eczema. One could have argued that the infections in this patient are actually secondary to the initial skin lesions. Moreover, the lack of autoimmune manifestations as well as the limited fungal infection did not support the diagnosis of typical CMCC. Nonetheless, this case highlights the need for a comprehensive genetic analysis in all cases that present with recurrent fungal infections regardless if it is primary or secondary.

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