To the editor:

**RAS-associated lymphoproliferative disease evolves into severe juvenile myelo-monocytic leukemia**

In juvenile myelomonocytic leukemia (JMML), activating RAS mutations are responsible for a hyperactive RAS/ERK signaling. Somatic codons 12-13-61 RAS mutations are described in cases of RAS-associated lymphoproliferative disease (RALD), believed to be a benign entity distinct from JMML. RALD features autoimmune cytopenias and lymphoproliferation secondary to a T-cell apoptosis defect, similar to autoimmune lymphoproliferative syndrome (ALPS). In RALD, the apoptosis defect is caused by a RAS/ERK-mediated downregulation of the proapoptotic BIM protein whereas in ALPS, the defect is caused by mutations of the death receptor FAS. Thus,
the same oncogenic hematopoietic RAS mutations are associated with different phenotypes, considered as distinct pathologies. We report a case of G13C KRAS mutation firstly leading to RALD and then evolving from an indolent to an aggressive form of leukemia.

The patient presented with autoimmune hemolytic anemia and thrombocytopenia, hepatosplenomegaly, and multifocal lymphadenopathy at age 5. He developed a colic B-cell lymphoproliferation at age 7.5. At age 9.5, he underwent splenectomy and received 4 anti-CD20 infusions. From then on, the Evans syndrome declined and the leukocyte numbers rose. At age 20, he presented with chest pain and leucocytosis. The situation evolved into fatal acute respiratory distress syndrome secondary to pulmonary leucostasis (Figure 1A).
The patient initially displayed classical RALD features. ALPS was ruled out after eliminating a FAS mutation. A somatic KRAS G13C mutation was found in all circulating hematopoietic cell subsets but not on primary derived fibroblasts (Figure 1B). Consistent with published data,2,4 BIM was downregulated in activated T cells (Figure 1C), leading to an in vitro defect of activated cell autonomous death (Figure 1D). Interestingly, lymph node histology showed Rosai-Dorfman–like features when biopsied at age 6, an aspect not yet described in RALD (supplemental Figure 1A-C on the Blood Web site).

After splenectomy, the patient started displaying classical JMML features with increasing peripheral myeloid cell numbers. In addition to ALPS features, the spleen showed an important immature myeloid colonization (supplemental Figure 1D-E). The blood smear showed circulating dysplastic neutrophils and abnormal monocytes (supplemental Figure 1F-G). The bone marrow was hypercellular with granulocytic hyperplasia without blast excess at ages 5 and 19 (supplemental Figure 1H-I). Spontaneous growth and hypersensitivity to granulocyte macrophage colony-stimulating factor of bone marrow progenitors were found. Rearrangement of the BCR-ABL fusion gene was always negative. The JMML evolved during a 10-year period as a “long survivor,” but the final stage was a classical feature seen in severe JMML.6

Autoimmunity has recently been reported in spontaneous re-mission cases of JMML with persistent RAS-mutated clones.7 We now show that RALD can be the initial presentation of a severe JMML. Moreover, the patient’s history shows that 1 RAS mutation associates with the 3 different possible phenotypes (RALD and indolent and severe JMML). We thus postulate that RALD and JMML are not distinct entities but a continuum with additional genetic or epigenetic events contributing to the clinical phenotype and evolution. Therefore, close monitoring of such patients is recommended, and further efforts are needed to elucidate the additional factors.

Nina Lanzarotti
INSERM UMR 1163, Laboratory of Immunogenetics of Pediatric Autoimmune Diseases, Paris, France
Paris Descartes-Sorbonne Paris Cité University, Imagine Institute, Paris, France
Département de Biothérapie, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France

Julie Bruneau
Paris Descartes-Sorbonne Paris Cité University, Imagine Institute, Paris, France
Service Anatomie et Cytologie Pathologiques, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France

Amélie Trinquet
Différenciation Lymphoïde Normale et Pathologique, Centre National de la Recherche Scientifique UMR8147, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France
Service d’Hématologie Biologique, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France

Marie-Claude Stolzenberg
INSERM UMR 1163, Laboratory of Immunogenetics of Pediatric Autoimmune Diseases, Paris, France
Paris Descartes-Sorbonne Paris Cité University, Imagine Institute, Paris, France

Bénédicte Neven
INSERM UMR 1163, Laboratory of Immunogenetics of Pediatric Autoimmune Diseases, Paris, France
Paris Descartes-Sorbonne Paris Cité University, Imagine Institute, Paris, France
Service d’Immunohématologie Adulte, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France

Julien Fregac
INSERM UMR 1163, Laboratory of Immunogenetics of Pediatric Autoimmune Diseases, Paris, France
Paris Descartes-Sorbonne Paris Cité University, Imagine Institute, Paris, France

Eva Levy
INSERM UMR 1163, Laboratory of Immunogenetics of Pediatric Autoimmune Diseases, Paris, France
Paris Descartes-Sorbonne Paris Cité University, Imagine Institute, Paris, France

Nadia Jeremiah
INSERM UMR 1163, Laboratory of Immunogenetics of Pediatric Autoimmune Diseases, Paris, France
Paris Descartes-Sorbonne Paris Cité University, Imagine Institute, Paris, France

Felipe Suarez
Cytokines, Hématopoïèse et Réponse Immune, CNRS UMR8147, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France
Service d’Immunohématologie Adulte, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France

Nizar Mahlaoui
Paris Descartes-Sorbonne Paris Cité University, Imagine Institute, Paris, France
Service d’Immunohématologie Adulte, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France
Centre de Référence des Déficits Immunitaires Héréditaires, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France

Alain Fischer
INSERM UMR 1163, Paris, France
Paris Descartes-Sorbonne Paris Cité University, Imagine Institute, Paris, France
Unité d’Immunohématologie et Rhumatologie Pédiatrique, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France

Aude Magerus-Chatinet
INSERM UMR 1163, Laboratory of Immunogenetics of Pediatric Autoimmune Diseases, Paris, France
Paris Descartes-Sorbonne Paris Cité University, Imagine Institute, Paris, France

Hélène Cavé
Département de Génétique, Assistance Publique-Hôpitaux de Paris, Hôpital Robert Debré, Paris, France
Université Paris-Diderot, Paris, France

Frédéric Rieux-Laucat
INSERM 2UMR 1163, Laboratory of Immunogenetics of Pediatric Autoimmune Diseases, Paris, France
Paris Descartes-Sorbonne Paris Cité University, Imagine Institute, Paris, France
Homozygous Southeast Asian ovalocytosis is a severe dyserythropoietic anemia associated with distal renal tubular acidosis

Southeast Asian ovalocytosis (SAO) is caused by a heterozygous 27-nucleotide deletion in SLC4A1 coding for band 3, the anion-exchange protein of the red cell membrane.1-3 This asymptomatic dominant trait is considered as a host genetic adaptation to malaria in Southeast Asia; homozygosity has not been described and is thought to be lethal.4 We report the first description of homozygous SAO in a child born to asymptomatic Comorian parents. After 22 weeks gestation, the male fetus presented with hydrops and severe anemia (hemoglobin [Hb] 2.9 g/dL) that was treated by utero transfusion. Common acquired or genetic causes of hydrops were excluded. A second transfusion 7 weeks later triggered bradycardia and emergency delivery. Since birth, a monthly transfusion program has kept the Hb level between 7 and 10 g/dL. At 3 months of age, distal renal tubular acidosis (dRTA) was diagnosed (hyperchloremic metabolic acidosis, increased urinary pH, and Ca²⁺ urinary excretion, but no nephrocalcinosis) and treated by oral sodium bicarbonate and potassium gluconate. Iron chelation using deferoxamine mesilate was started at 6 months of age because of high ferritinemia.

Interestingly, dyserythropoiesis was not described in the previously reported human cases of homozygous band 3 mutation but was observed in a zebra fish carrying mutations in the ortholog slc4a1.6,7 Here, dyserythropoiesis was not accounted for by the absence of band 3 because we showed that SAO band 3 was expressed on the proband red cells. Using confocal microscopy and selected antibodies, we could differentiate the proband from the donor cells and demonstrate that homozygous SAO band 3 is folded sufficiently well to insert into the membrane (Figure 1D).8

As expected, the child presented with dRTA. In the kidney, an N-terminally truncated band 3 (kAE1) is expressed in α-intercalated distal tubular cells and contributes to the acidification of urine. Total loss of band 3 results in dRTA, as reported in homozygous band 3 Coimbra.9 Homozygous SAO has a similar effect because SAO band 3 cannot exchange anions.9,10 The child is now 3 years old. His psychomotor development is normal, as well as his height and weight growth. He does not present neurologic complications, increased susceptibility to infection, or thromboembolic disorder; however, the prognosis is uncertain. Bone marrow transplantation can be considered because the disease is as severe as thanassemia major. Finally, a prenatal diagnosis can be proposed for a future pregnancy in this couple, and in case of homozygous SAO, medical termination of pregnancy remains an alternative.

Véronique Picard
Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre, Service d’Hématologie Biologique, Le Kremlin Bicêtre, France

Alexis Proust
Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre, Service d’Hématologie Biologique et Plateforme de Génétique Moléculaire, Le Kremlin Bicêtre, France

Marion Eveillard
Department of Hematology, Nantes University Hospital, Nantes, France

Joanna F. Flatt
Bristol Institute for Transfusion Sciences, National Health Service Blood & Transplant, Bristol, United Kingdom

References


© 2014 by The American Society of Hematology

To the editor:
RAS-associated lymphoproliferative disease evolves into severe juvenile myelo-monocytic leukemia

Nina Lanzarotti, Julie Bruneau, Amélie Trinquand, Marie-Claude Stolzenberg, Bénédicte Neven, Julien Fregeac, Eva Levy, Nadia Jeremiah, Felipe Suarez, Nizar Mahlaoui, Alain Fischer, Aude Magerus-Chatinet, Hélène Cavé and Frédéric Rieux-Laucat