



Letter

X-linked agammaglobulinemia in a child conceived using a donor egg: a medicolegal quandary

X-linked agammaglobulinemia (XLA) is a primary immunodeficiency in which mutation of Bruton tyrosine kinase (BTK) leads to B-lymphocyte differentiation arrest, failure to generate immunoglobulins, and recurrent bacterial infections that can be life threatening.¹ Our patient was a 3-year-old male full-term product of an anonymous donor egg pregnancy. He was initially diagnosed with juvenile idiopathic arthritis and subsequently found to have a novel mutation causing XLA. This is the first report, to our knowledge, of any primary immunodeficiency, including XLA, diagnosed in a child conceived using a donor egg. We present his condition and review the ethical dimensions of his case with his parents' consent.

At 2 years of age, he presented to a rheumatology clinic with a 3-month history of limp and left lower extremity pain. Joint radiographic results were within normal limits and without effusion. Antinuclear antibody, rheumatoid factor, and HLA-B27 were not detected. His erythrocyte sedimentation rate and C-reactive protein values were mildly elevated (erythrocyte sedimentation rate 12 mm/h, normal <10 mm/h; C-reactive protein 2 mg/dL, normal <0.9 mg/dL). The patient was diagnosed with seronegative oligoarticular juvenile idiopathic arthritis. Methotrexate and etanercept treatment relieved his joint disease, but he developed frequent minor infections requiring antibiotics.

At 3 years of age, he presented to an emergency department with 2 weeks of intermittent fever and mild upper respiratory symptoms. He had recovered from balanitis just 3 weeks previously. His physical examination showed a forehead cellulitis, acute otitis media, and no lymphadenopathy. He was severely neutropenic, with no neutrophils detected on his complete blood cell count. Serum immunoglobulins were undetectable. Lymphocyte enumeration showed B-cell lymphopenia (CD19⁺ <1%, absolute CD19 1 cell/ μ L). BTK protein was detected by flow cytometry; however, BTK genomic sequencing showed a single thymidine deletion that produced a frameshift mutation and a premature termination codon (c1774delT; g100494972delT), thus confirming the diagnosis of XLA. This novel mutation has not been reported previously in the literature or in BTK gene mutation databases. His infections responded well to intravenous treatment with cefepime, vancomycin, and immunoglobulin (0.6 g/kg), and his persistent XLA-associated neutropenia responded well to filgrastim (5 μ g/kg).² We have highlighted this case because of the clinical and legal complexities it raised.

First, the association between inflammatory and immunodeficiency disorders poses a challenge to the management of arthropathies. Although nearly 20% of patients with XLA report

painful joints, only 7% are given the diagnosis of arthritis.³ In retrospect, this patient's arthropathy might have been a consequence of his primary immunodeficiency or caused by opportunistic infections of the joints, and careful examination of his laboratory results might have identified his primary immunodeficiency sooner. For instance, on 2 occasions before his XLA diagnosis, the difference between his total protein and serum albumin was less than 200 mg/dL, consistent with hypogammaglobulinemia. Fortunately, this patient avoided the potentially disastrous complications of immunosuppressive treatment for a person with a primary immunodeficiency.

Second, because the mutation causing XLA is usually inherited from a maternal carrier and rarely occurs *de novo*, a patient's family typically is offered genetic counseling and appropriate genetic testing.⁴ However, this process was legally confounded by the use of an anonymous egg donor in this case.

The discovery of heritable diseases in donor-conceived children is likely to occur with increasing frequency. Clinical human egg donation doubled from 1995 through 2006.^{5,6} In 2012, nearly 20,000 assisted reproductive technology (ART) cycles involved the use of donor eggs and resulted in more than 9,000 live births.⁷ Despite reports of genetic disease transmission, comprehensive genetic screening of gamete donors is not required by law. The American Society for Reproductive Medicine has published guidelines for gamete and embryo donation that include recommendations for (1) genetic screening of gamete donors, (2) an agreement by the donor to disclose health developments that could affect the recipient, and (3) a system for reporting the discovery of a heritable disease in a donor-conceived child:

In the event that a previously unidentified heritable disease is encountered in a child produced from anonymous donation, the donor as well as the recipient of the donated oocytes should be tested and the donor should be prohibited from further donation until the results of such testing are known. If the donor is found to be the carrier for the heritable disease, all women who received oocytes from that donor as well as the clinics performing the procedures should be notified and counseled.⁸

Compliance with American Society for Reproductive Medicine guidelines remains voluntary, and no centralized system for maintaining permanent donor records or reporting adverse postnatal events exists in the United States. Instead, donors and recipients rely on the heterogeneous policies and procedures of independent donation agencies and state regulators.

Donors have several compelling reasons to learn about heritable conditions diagnosed in children produced by their gametes. The

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diagnosis could affect their own health or the health of their existing children, and it could inform future decisions about their own reproduction. Furthermore, a gamete donor can provide gametes to multiple families, and each of those families stands to benefit from knowledge of a genetic diagnosis.⁹

Gamete donation in the United States is frequently governed by contracts that circumscribe the nature and direction of communication between parties.¹⁰ The contract in this case only required disclosure of health developments by the donor but not by the recipients. Lacking guidance from the pre-existing agreement, we nevertheless believed we had an obligation to inform the donor about the diagnosis of a life-threatening primary immunodeficiency that could affect her offspring and any other families who received her eggs. Without sharing any identifying information, we contacted the donation agency. They recommended that we encourage our patient's parents to contact the agency directly so that the agency could act as a go-between, allowing impactful genetic information to reach the donor while still honoring the privacy promised to all parties.

In the current practice of ART using donor gametes in the United States, decentralized record keeping and contractual restrictions could prevent impactful genetic diagnoses from being disclosed to donors or recipients. This case report illustrates the challenge posed by the diagnosis of an X-linked disease in a donor egg-conceived child and the obvious advantage a centralized donor gamete record system would provide to donors and recipients alike. Consideration of the obligations held by donors and recipients for sharing information that pertains to each other's health should inform future gamete donor agreements and national ART policy.

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