**Abstract**

Pediatric-onset inflammatory myositis (IM) and systemic lupus erythematosus (SLE) are rare inflammatory diseases. Both result from the complex interaction of genetic and environmental factors. An increasing number of Mendelian conditions predisposing to the development of SLE have been recently identified. These include monogenic conditions, referred to as the type I interferonopathies, associated with a primary upregulation of type I interferon (IFN), a key cytokine in the pathogenesis of SLE and some cases of IM. Here, we report on a pediatric-onset inflammatory overlap phenotype in a 6-year-old girl who was shown to carry mosaic tetrasomy 9p. The patient presented with myositis overlapping with lupuslike features. Myositis was characterized by a proximal muscular weakness and HLA class I antigen myofiber overexpression on muscle biopsy. Lupus-like manifestations consisted of pericarditis, pleuritis, and positive antinuclear and anti-SSA (Sjögren-syndrome A) antibodies. Complete remission was achieved with corticosteroids and mycophenolate mofetyl. Analysis of tetrasomy 9p showed mosaic tetrasomy in the 9p24.3q12 region, including the type I IFN cluster, and increased expression of IFN-stimulated genes. These data suggest that mosaic tetrasomy 9p can be associated with an upregulation of type I IFN signaling, predisposing to inflammatory myositis and lupus-like features. Thus, unexplained muscle or other organ involvement in patients carrying mosaic tetrasomy of the 9p IFN cluster of chromosome 9p should lead to the search for IM and/or lupuslike disease, and karyotype should be performed in patients with SLE or IM with mental retardation.
exudate containing a majority of lymphocytes and an increased number of macrophages and mesothelial cells, respectively. Pericardial biopsy revealed lymphocytic infiltration. There was no evidence of infection. Three pulses of methylprednisolone, followed by an oral course of steroids in combination with mycophenolate mofetyl, resulted in a complete clinical remission.

Comparative genomic hybridization arrays were used to better specify the breakpoints of the tetrasomy. The comparative genomic hybridization platform used was a single-nucleotide polymorphism microarray analysis performed by using the Illumina HumanHap300 BeadChips platform (Illumina, Inc, San Diego, CA). Data were analyzed with Genome Studio software (Illumina, Inc, San Diego, CA). Probe positions were established for all cases by using the Genome Browser Assembly hg19 (National Center for Biotechnology Information Build 37; http://genome.ucsc.edu/cgi-bin/hgGateway). Mosaic tetrasomy of 9p resulted in a triplication of the 9p24.3q12 including 495 genes, known to be IFN-stimulated. The expression of IFN-stimulated genes, a so-called IFN signature, was assessed from total RNA extracted from whole blood by using a PAXgene RNA isolation kit (PreAnalytix GmbH, Switzerland).

**DISCUSSION**

We report on a patient carrying a mosaic tetrasomy of 9p who presented with an overlap myositis. Myositis was characterized by a proximal muscular weakness and HLA class I antigen myofiber overexpression on muscle biopsy. Overlap features consisted of lupus manifestations comprising pericarditis, pleuritis, and positive ANAs and anti-SSA antibodies.

Tetrasomy 9p has a highly variable phenotype due to the position of the breakpoints and number of cell lineages affected, resulting in differential levels and distribution of mosaicism. Tetrasomy 9p mosaicism commonly leads to facial dysmorphology associated with moderate to severe mental disability, mild growth retardation, renal and skeletal abnormalities, and congenital heart disease. However, normal phenotypes are also possible. This report identifies, for the first time to our knowledge, mosaic tetrasomy of 9p as predisposing to the development of IM, which is associated with an upregulation of type I IFN activity.

Type I IFN plays a key role in the pathogenesis of SLE and some forms of IM. In both diseases, type I IFN genes are upregulated, and serum IFN-α is a biomarker of disease activity. The genes encoding for the 13 different IFN-α protein isoforms are found together in a cluster on chromosome 9p22. In our patient, mosaic tetrasomy 9p resulted in a triplication of the 9p24.3q12 region, which includes a cluster of 17 genes encoding for type I IFN.
As shown by the observation of an IFN signature, it appears that mosaic tetrasomy 9p results in an increased expression of genes induced by IFN, which is in accordance with the findings of Zhuang et al. who reported SLE-like disease associated with elevated levels of IFN-α/β in 2 patients with a trisomy of 9p–containing type I IFN cluster. Our report supports the hypothesis that several copies of the type I IFN cluster result in high levels of type I IFN due to a gene-dosage effect, and hence an increased susceptibility to some autoimmune diseases. Thus, we hypothesize that the presence of overlap myositis in our patient with tetrasomy of 9p reported here was related to the presence of 4 copies of the type I IFN gene cluster, and was not coincidental. However, the observation of a single patient is a limitation of our study, and additional reports are required to confirm the relationship between the chromosomal aneuploidy and autoimmunity.

Pediatric-onset overlap myositis is characterized by the association of juvenile DM (dermatomyositis) or polymyositis with another autoimmune disease, such as SLE, scleroderma, juvenile idiopathic arthritis, inflammatory bowel disease, type 1 diabetes mellitus, or celiac disease. An increasing number of Mendelian conditions predisposing to the development of pediatric SLE have been identified. To date, 3 major molecular pathways have been involved in the development of monogenic SLE: (1) a disturbed clearance of apoptotic material in complement deficiencies, leading to lupus in association with a predisposition to infections; (2) an upregulated production of type I IFN in type I interferonopathies, including Aicardi-Goutières syndrome, ACP5 gene mutations causing SLE associated with a skeletal dysplasia, mutations in DNASE1L3 associated with lupus nephritis, and STING (Stimulator of interferon genes)-associated vasculopathy with onset in infancy (SAVI); and (3) defective T-cell apoptosis coupled with dysregulated B-cell proliferation, which results from protein kinase Cδ deficiency, leading to Mendelian lupus in association with lymphoproliferative syndrome due to increased B-cell proliferation. Until now, ACP5 gene mutation was the only known monogenic condition associated with the development of IM. The present report suggests that mosaic tetrasomy of 9p might also predispose to this disease.

In conclusion, our report suggests that mosaic tetrasomy 9p predisposes to IM and lupus-like features. Our data implicate a dysregulation of type I IFN signaling due to the chromosomal aneuploidy. These observations emphasize that lupus-like disease and/or IM should be considered in patients with tetrasomy of 9p presenting with an acquired muscle or other organ involvement and that genetic studies should be performed in patients with mental retardation who develop IM and/or lupus-like features.

ACKNOWLEDGMENTS

We thank Dr Gillian I. Rice for her help and contribution, in particular for performing expression analyses of type I IFN–stimulated genes.

ABBREVIATIONS

ANA: antinuclear antibody
IFN: interferon
IM: inflammatory myositis
SLE: systemic lupus erythematosus
SSA: Sjögren-syndrome A

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*Pediatrics* 2015;136:e544; originally published online July 27, 2015;
DOI: 10.1542/peds.2015-0724

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