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Short report

Reactive lymphoid hyperplasia in association with 22q11.2 deletion syndrome and a *BRCA2* mutation☆

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ABSTRACT

We report an adult male with 22q11.2 deletion syndrome and a germline *BRCA2* mutation who developed T-cell monoclonal lymphoid proliferation involving the skin and a polyclonal proliferation of a retroperitoneal lymph node without any identifiable infectious and inflammatory causes. This is the first report of reactive lymphoid hyperplasia in the setting of co-occurrence of 22q11.2 deletion syndrome and a *BRCA2* mutation. Further cases with a similar presentation should be reported and studies should be directed to identify the possible mechanisms involved.

1. Introduction

Common clinical manifestations of chromosome 22q11.2 deletion syndrome (22q11DS), also referred to as velocardiofacial syndrome or DiGeorge syndrome, include conotruncal heart abnormalities, palatal anomalies, hypoparathyroidism, immune deficiency and cognitive deficits [23,24]. Although most patients given the diagnosis of DiGeorge syndrome have a hemizygous 22q11.2 deletion [20], other causes for DiGeorge syndrome include maternal diabetes, fetal exposure to alcohol, deletions of chromosome 10p and deletion of chromosome 17p13 [1,7–9]. Whether or not it is associated with a 22q11.2 deletion, DiGeorge syndrome is classified by immunologists into complete and partial forms depending on the absence or presence respectively, of thymic function [9]. The majority of individuals with 22q11DS has partial DiGeorge syndrome, with <1% having complete form. For the purpose of this paper, we will focus on the risk of malignancy/lymphoid proliferation in individuals with a 22q11.2 deletion, rather than individuals who have DiGeorge syndrome due to other causes.

An increased incidence (0.9%) of a variety of malignancies has been reported in patients with 22q11DS [12], particularly in patients with severe immune defects. Immune deficiency in 22q11DS is variable, ranging from profound deficiency including abnormalities in humoral immunity and autoimmunity to completely normal function [3,11,13,26].

BRCA2 (Breast cancer 2 gene) is a tumor suppressor gene located in chromosome 13q12.3. Mutations in this gene, in conjunction with *BRCA1*, are responsible for the largest number of inherited breast cancers and a large proportion of ovarian cancers. Additionally, individuals with *BRCA2* mutations have an increased risk for lymphomas and leukemias [25,29].

Here we report an adult male with 22q11DS and a *BRCA2* mutation who has had evidence of lymphoid hyperplasia in more than one tissue and we believe that co-occurrence of these may have predisposed him to the excessive lymphoid proliferation. This report would enhance clinicians' awareness and may stimulate further research into the pathogenesis of such lymphoid proliferation.

2. Case report

A 24 year-old gentleman, followed in the Genetics clinic for 22q11DS, developed a rash characterized by erythematous, pinpoint papules coalescing into plaques on the medial aspect of both thighs, with the right side more affected. A slight orangish hue was noted on these plaques, and a prominent varicosity was

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observed within the right thigh lesion. Microscopic and immunohistochemical analyses of the biopsied lesion showed an atypical lymphoid infiltrate. T-cell gamma chain PCR detected a monoclonal T-cell population. The possibility of cutaneous T-cell lymphoma (CTCL) was considered. No monoclonal or phenotypically abnormal T-cell populations were detected in peripheral blood. Subsequently, the rash resolved spontaneously in the span of a month.

Four months later, a routine abdominal ultrasound to look for nephrocalcinosis (he was on calcium supplementation for hypoparathyroidism) revealed an ovoid mass in the region of the head of pancreas. An abdominal MRI scan confirmed the presence of a 4.4 × 3.4 cm mass, right and inferior to the pancreatic head that enhanced with contrast; however, he did not have any signs and symptoms of pancreatitis. The microscopic and immunohistochemical findings of an ultrasound guided fine needle aspirate from the mass were consistent with reactive lymphoid hyperplasia. Evaluation for possible infectious causes of lymphoid hyperplasia, including typical and atypical tuberculosis, Bartonella, HIV, CMV, EBV and other viral infections was negative. Surgical resection was performed due to its unusual location, the large size, and the low sensitivity of needle biopsy sampling. The pancreas appeared normal during surgical exploration. Microscopic analysis and flow cytometric immunophenotyping of the resected mass confirmed reactive lymphoid hyperplasia. No monoclonal B or T-cell populations and no phenotypically abnormal T-cells were detected. Thus the mass was determined to be a retroperitoneal lymph node with no evidence of malignant proliferation.

The patient received a formal evaluation of his immune system. A prior assessment performed elsewhere when he was 14 years of age showed that he had normal levels of immunoglobulins (IgG 1612 mg/dl, IgA 194 mg/dl, and IgM 152 mg/dl) with a "mild decrease in the percentages of total T-cells and $CD8^+$ T-cells". He was also noted to have protective antibody responses to measles and mumps immunizations. At 17 years of age he had normal levels of antibodies to 6 of 6 pneumococcal polysaccharide serotypes tested. After identification of the monoclonal T-cell population in the skin at 24 years of age, the patient underwent repeat evaluation of his T-cells (Table 1). The $CD4^+$:$CD8^+$ T-cell ratio was unusually elevated (3.8, normal = 2) because of the low $CD8^+$ T-cell numbers. The patient had normal T-cell proliferative responses to mitogens (Table 2). He demonstrated a low but adequate T-cell proliferative response to *Candida* antigen; his T-cell proliferative response to tetanus toxoid, however, was less than 5-fold greater than background after booster immunization (abnormal).

Table 1
Lymphocyte enumeration study results in our patient.

Cell type or CD marker	Patient		Control (%)	Normal percentages (absolute numbers)
	Percentage (%)	Absolute number (cells/mm^3)		
T-cells				
Total $CD3^+$	46.2	765	74.0	67.9–81.0 (1019–3240)
$CD4^+$	37.0	613	56.1	39.2–50.8 (588–2032)
$CD8^+$	9.8	162	17.5	18.9–32.5 (284–1300)
$CD45RA^+$ $CD62L^+$ (naïve T-cells)	32.7	250	43.1	NA[a]
NK cells				
$CD16^+$	33.2	550	12.3	3.5–14.5 (53–580)
$CD56^+$	32.7	542	15.1	4.0–13.9 (60–556)
B-cells				
$CD19^+$	15.6	258	8.8	6.9–14.9 (104–596)

[a] NA – Not available.

2.1. BRCA2 testing and family history

Neither of the patient's parents had a 22q11.2 deletion. His paternal aunt and grandmother have had breast cancer. The paternal side of the family is of Ashkenazi Jewish ancestry. The patient's father, paternal aunt and grandmother were found to have one of the Ashkenazi Jewish founder mutations in the *BRCA2* gene; 6174delT, resulting in premature truncation of the protein at amino acid position 2003. The patient was tested after the abdominal lymph node was detected and was found to have the same mutation.

3. Discussion

We describe the first report of the synchronous presence of 22q11DS and a *BRCA2* mutation in a male who developed excessive lymphoid proliferation involving the skin and the lymph nodes. Even though the *BRCA2* mutation found in our patient has been described in association with lymphomas [25,29], no reports are available that describe this mutation with either non-malignant lymph node proliferation or CTCL. Similarly, no reports of benign lymphoid proliferation or CTCL with 22q11DS currently exist. We hypothesize that the excessive lymphoid hyperplasia in our patient may have been due to a combined effect of 22q11DS and the *BRCA2* mutation.

A review of the literature of malignancies in 22q11DS shows that the terms 22q11DS and DiGeorge syndrome have been used interchangeably. It remains unclear in many of the reports of malignancies whether or not the patients had a 22q11.2 deletion. For example, a few cases of DiGeorge syndrome with lymphomas [10,19,21] and other malignancies [2,18,27] have been described without confirmation of the presence of a 22q11.2 deletion. Nonetheless, there seems to be an increased incidence of malignancies in 22q11DS as evidenced by several reports [12,15,16,22]. Multiple factors are believed to be responsible for the increased risk for malignancies in 22Q11DS, as discussed below.

Patients with severe immunodeficiency or T-cell defects have an increased risk for malignancies, particularly B cell lymphomas which are thought to be related to Epstein–Barr virus (EBV) infection; however, our patient did not have evidence of an EBV infection. Our patient's immune evaluation revealed subtle abnormalities in his thymic function (as assessed by the low circulating naïve T-cell percentage) and T-cell function. In particular, the low T-cell proliferative response to tetanus toxoid, even after booster immunization, suggests that his T cells may have difficulty responding appropriately to various antigens, such as ones associated with infections, malignancies, and autoimmune diseases. In fact, the presence of autoimmune thrombocytopenia in our patient provides further evidence for immune dysregulation. Both $CD8^+$ T cells and NK cells are felt to play a significant role in tumor surveillance. The percentage and absolute number of $CD8^+$ T cells in the patient are both low; however, they appear to be compensated by an increase in NK cells. Thus, we suspect that immune dysregulation may be contributing to the lymphoid proliferation in our patient.

Altered functions of some of the genes that are located in the commonly deleted region in 22q11DS have been hypothesized to be associated with malignancy. The common deletion includes the catechol-O-methyltransferase (*COMT*) gene, altered function of which has been known to impair the detoxification of certain environmental carcinogens, and thus *COMT* is speculated to have a role in the causation of malignancies in 22q11DS [12]; however,