

Common variable immunodeficiency with CD4+ T lymphocytopenia and overproduction of soluble IL-2 receptor associated with Turner's syndrome and dorsal kyphoscoliosis

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Abstract

An unusual combination of common variable immunodeficiency (CVID) and Turner's syndrome in a Saudi woman aged 20 years is presented. In addition to panhypogammaglobulinaemia, the patient had CD4+ T lymphocytopenia; however, there was evidence of in vivo activation of T cells and overproduction of soluble interleukin 2 receptor in culture supernate. Mantoux test was positive, but lymphoblastic response to non-specific mitogen was impaired. Immunogenetically the patient was HLA-DR3 positive and karyotypically she was a mosaic (45XO/46XX) with ring X chromosome (46Xr(X)). The presence of severe kyphoscoliosis was possibly related to ring X chromosome. This case highlights the grave consequences of the delayed diagnosis of immunodeficiency and emphasises the heterogeneous nature of CVID.

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Keywords: common variable immunodeficiency; Turner's syndrome; CD4+ T lymphocytopenia; soluble interleukin 2 receptor

Common variable immunodeficiency (CVID) is a rare disorder with an estimated prevalence of 1 per 100 000 population. The hallmark of the disease is hypogammaglobulinaemia affecting at least two of the three major serum immunoglobulin isotypes.¹ Typically patients present with recurrent sinopulmonary infections as well as a wide variety of autoimmune and neoplastic disorders. Precise aetiopathogenesis is unknown, but retroviral infection, B cell anergy, deficiency of several enzymes (such as 5'-nucleotidase, glutathione, and dipeptidyl peptidase IV), abnormality of T cell subsets, T cell dysfunction, deficient antigen-TcR coupling, and abnormal cytokine production (such as decreased synthesis of interleukin (IL)-2, interferon τ , IL-4, IL-5, IL-9, or increased production of IL-4, IL-6, and tumour necrosis factor α) have been implicated.¹⁻³ Recently a subset of CVID with decreased CD4:CD8 ratio and raised CD8+ suppressor T cells has been identified¹; within this subset there is a rare occurrence of CD4+ T lymphocytopenia (< 20% of total lymphocytes) affecting mainly the virgin (CD4+, CD45RA+) helper T cells.⁴

The association of Turner's syndrome (a sex chromosomal disorder with female phenotype,

XO karyotype, short stature, and sexual infantilism) and autoimmune endocrinopathy is well recognised⁵; however, CVID has been reported only once in association with this syndrome.⁶

We report an unusual association of CVID with CD4+ T lymphocytopenia, overproduction of soluble IL-2 receptor (sIL-2R), and skeletal malformation in a patient with Turner's syndrome. To the best of our knowledge, this is the first documentation of such an unusual presentation, at least from the Middle East.

Case report

A Saudi woman aged 20 years presented with a history of recurrent chest and ear infection, and chronic diarrhoea since early childhood, she also had sickle cell and α thalassaemia traits, and primary amenorrhoea. On clinical examination, the patient was found to be of short stature with prepubertal appearance (height 118 cm, weight 20 kg). There was digital clubbing but no cyanosis. Eyes showed mild inflammation; there was no lymphadenopathy. The patient had marked dorsal kyphoscoliosis with convexity towards the left side. Chest examination showed partial breast development and auscultation revealed crepitation.

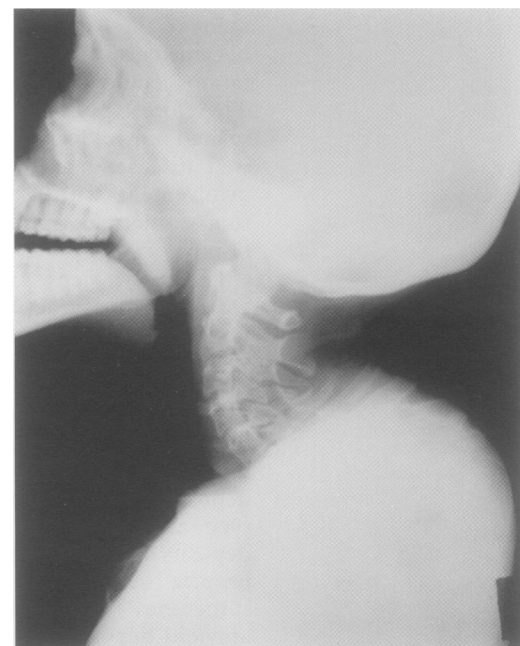


Figure 1 Lateral view of the cervical spines showing kyphosis in the lower region.

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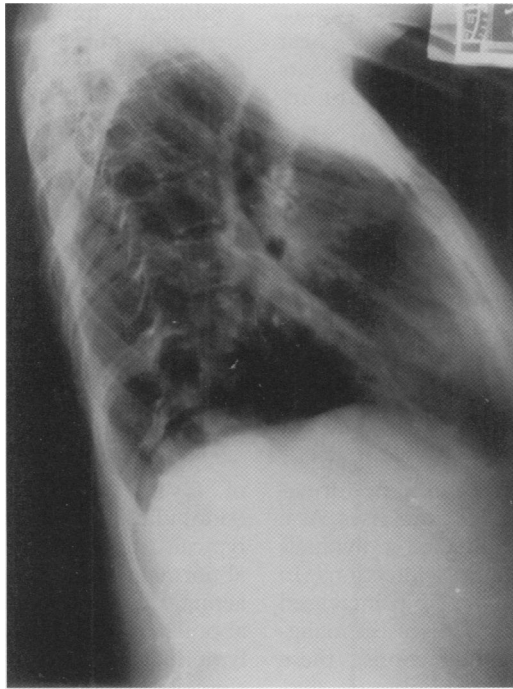


Figure 2 Lateral view of dorsal spines showing kyphosis.

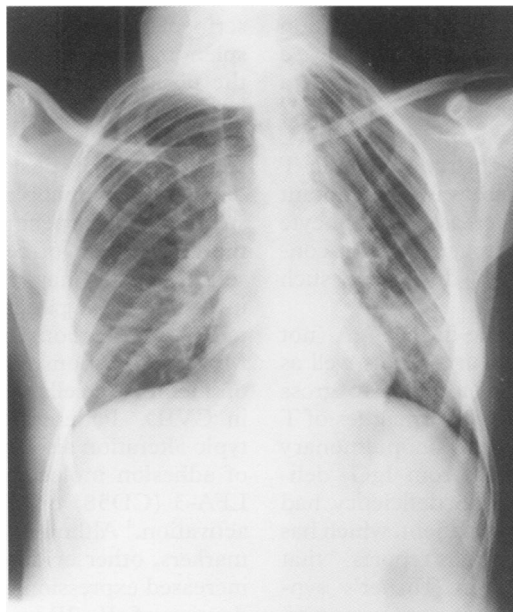


Figure 3 Anteroposterior chest radiogram showing distortion of thoracic cage and hilar calcification.

Cardiovascular and abdominal examination was normal. The patient was partially deaf, mentally slow, and had been able to achieve not more than primary education.

INVESTIGATIONS

Radiology

Radiography of the spine showed kyphoscoliosis involving the lower cervical and upper dorsal spine leading to distortion of the thoracic cage and crowding of the ribs on the left side. There were bilateral bronchiectatic changes with calcified areas in both hilar regions suggestive of healed tubercular lesions (figs 1-3).

Ultrasonography of the abdomen showed a bulky spleen for stature; the left ovary was normal but the right ovary was not visible, and the uterus was reduced in size.

Laboratory investigation

Routine biochemical profile was normal; sex hormone analysis was not available. Routine haematological indices were within normal range except for microcytosis and hypochromia because of thalassaemic trait. Haemoglobin electrophoresis showed 66.7% HbA₁, 31.9% HbS, and 1.4% HbA₂.

Tuberculin test

Mantoux was positive in 2IU of PPD, the size of induration after 72 hours being 14 mm.

Cytogenetic study

Buccal smear was negative for sex chromatin and chromosomal analysis showed mixoploidy of 45XO/46XX compatible with mosaic monosomy X. In addition, chromosomal structural abnormality (ring X chromosome) was noted.

Microbiological study

Sputum culture revealed growth of *Haemophilus influenzae*, and stool examination showed *Giardia lamblia* and *Trichomonas hominis*. ELISA test was negative for human immunodeficiency virus (HIV) infection.

Immunological study

Rate nephelometry showed marked reduction of all three major immunoglobulin classes (IgG 112 g/l, IgA 13 g/l, IgM 16 g/l). Serum isohaemagglutinin was severely reduced; as the patient was B⁺, anti-A was detectable only in undiluted serum (normal for age > 1:16). Immunofluorescence and haemagglutination tests for organ and non-organ specific autoantibodies were negative.

Lymphocyte subsets—Flow cytometry for B and T lymphocytes and their subsets showed CD3⁺ T lymphocytes 82% (3040/μl), CD3⁺ CD4⁺ helper T cells 13% (480/μl), CD3⁺ CD8⁺ suppressor/cytotoxic T cells 71% (2630/μl), CD4⁺:CD8⁺ ratio 0.2, natural killer cells (CD3⁻, CD16⁺, CD56⁺) 7% (260/μl), CD19⁺ B cell 3% (110/μl), and activated T (CD3⁺, DR⁺) 21%.

In vitro lymphocyte stimulation study

Peripheral mononuclear cells were separated on a discontinuous density gradient and cultured in microtitre plate suspended in RPMI 1640 (10⁶ lymphocytes/ml). Standard techniques were used for blastic transformation using phytohaemagglutinin (at three different concentrations 10, 15, and 20 μl/100 μl cell suspension). The transformation index in the patient's sample was 50% of the control lymphocytes (tested at the same time). Soluble IL-2 receptor (sIL-2R) was measured by ELISA (Genzyme, California, USA) in the culture supernate; it was 5900 pg/ml (control < 100 pg/ml; 10⁶ lymphocytes/ml were used).

HLA study

Class I and class II histocompatibility antigens were tested by NIH complement dependent microlymphocytotoxicity technique. The patient was HLA-DR3+ve.¹

Audiogram

Audiogram showed bilateral conductive hearing loss, a grommet had been inserted three years previously but was removed because of repeated ear infection.

TREATMENT

On the basis of cellular and humoral studies the patient was diagnosed as having CVID; she received intravenous γ globulin (300 mg/kg), co-amoxiclav, and metronidazole. A course of chest physiotherapy was also given. The patient had gained 1.5 kg during her three week stay in hospital.

Discussion

CVID is a heterogeneous group of disorders having in common defective antibody formation, particularly IgA and IgG subclasses. As a consequence, many of the affected individuals are prone to recurrent bacterial infections. In addition, such individuals exhibit increased susceptibility to autoimmune diseases, malignancy, and certain viral infections; these features suggest a generalised immune dysregulation rather than simple humoral immunodeficiency.¹

Low serum immunoglobulin in association with Turner's syndrome does not show a consistent pattern. Wood *et al*⁷ noted a decrease in IgM only, whereas Cacciari *et al*⁵ found modest reductions in both IgG and IgM. In addition they found slight reductions in T and B cell populations; there was concomitant increase in null cells and decreased lymphocyte response to non-specific mitogens. On the contrary, one report failed to document such abnormalities.⁸

The present case is unique in that IgA (not previously documented in Turner's) as well as IgG and IgM were low, in addition to gross qualitative and quantitative abnormalities of T cells. Furthermore, recurrent sinopulmonary infection, probably resulting from IgG₂ deficiency as part of general IgG deficiency had been a major problem in this patient, which has not been highlighted in previous reports⁵⁻⁸ that discuss immunodeficiency in Turner's syndrome only in the context of autoimmunity. Whether humoral or cellular immunodeficiency in our patient was coincidental or causally associated with Turner's syndrome is not known, but there are now at least five well established X linked immunodeficiency diseases with known loci including Wiskott-Aldrich syndrome, X linked severe combined immunodeficiency (X SCID), X linked agammaglobulinaemia, chronic granulomatous disease, and X linked hyper-IgM syndrome.⁹ The gene for the γ chain of the IL-2 receptor located on Xq is mutated in X-SCID¹⁰; as this γ chain is common to receptors of some other interleukins such as IL-4, IL-7, IL-9, and IL-15, the X chromosome plays a significant role in immune regulation.

CD4+ T lymphocytopenia mimicking AIDS has been documented in one case of CVID.¹¹ Reduction of CD4+ T lymphocytes to < 20% of total T cells is also a feature of idiopathic CD4+ T lymphocytopenia, but in this

syndrome¹² immunoglobulin concentrations are usually normal. Our patient was HIV negative and, at least at the time of presentation, there was no evidence of other viral infection, generalised sepsis, acute pyelonephritis, or disseminated fungal infection or history of immunosuppressive therapy. All of these are known to cause a severe reduction in the CD4+ population. Increased production of sIL-2R has been previously reported in CVID.¹³ It is also a feature of disease activity in rheumatic disorders and several other inflammatory diseases, and is believed to play an immunomodulatory role¹⁴; whether this was responsible in part for the cellular immunodeficiency in our patient is a matter of conjecture.

The present patient represents a unique case of CVID; although clinical manifestations (sinopulmonary infection and diarrhoea) were typical, the combination of immunological abnormalities such as panhypogammaglobulinaemia, slight reduction of B cells (described in about 20% of CVID cases),¹³ selective CD4+ T lymphocytopenia, increased CD8+ T suppressor cells, and decreased CD4+:CD8+ ratio were unusual.

Reduced CD4+:CD8+ ratio has been described in a subset of CVID characterised by splenomegaly and skin anergy.¹³ We consider the positive tuberculin test in this patient an important variation. This patient may belong to a new subgroup or a variant of the existing subgroup. The positive tuberculin test but depressed lymphoblastic transformation response to non-specific mitogen indicates that the impairment of cell mediated immunity is selective and may explain absence of viral infection in our patient, despite reports of certain viral infections in some cases of CVID.¹ Moreover, response to recall antigens depends on memory T cells that are known to be raised in CVID.⁴ Patients with this immunophenotypic alteration also show increased expression of adhesion molecules ICAM-1 (CD54) and LFA-3 (CD58) on T cells indicating in vivo activation.⁴ Although we did not test for these markers, other evidence of activation, such as increased expression of HLA-DR and overproduction of sIL-2R were seen. Although we did not investigate the relative importance of T helper 1 and T helper 2 cytokine responses in this patient, it would be relevant to include these in future studies on such cases. Furthermore, it is now known that the γ chain of the IL-2 receptor coded by a gene located at Xq(13.1) is found in multiple cytokine receptor complex¹⁰ and is shared by the receptors for IL-4, IL-7, IL-9, and IL-15. It would be interesting to examine expression of this common gene product at cytoplasmic level either in terms of the finished product or at the level of mRNA.

Genetic susceptibility to CVID has been previously reported; many patients show increased prevalence of HLA-DR3, deletion of C4A gene, and presence of valine or alanine at position 57 in HLA-DQ β chain.¹ It is of interest that our patient was also DR3 positive. We did not test for deletion of C4A, but we will include this in our protocol for future study. As

DR3 is often associated with autoimmunity, any patient with CVID with this HLA haplotype requires close follow up.

On reviewing the literature, we found only one case report of CVID in Turner's syndrome in which the presenting feature was recurrent sinopulmonary infection.⁶ To the best of our knowledge this is the second case report showing this interesting combination; in addition, we report a previously undocumented association of kyphoscoliosis. This malformation is probably related to ring X chromosome; this chromosomal structural abnormality is not a common finding in Turner's syndrome,¹⁵ but when present, it is usually associated with severe phenotype.¹⁶ If further cases come to light, this combination of immunodeficiency, skeletal malformation, and structural chromosomal aberration might constitute a novel syndrome.

As diagnostic delay in this case had led to serious morbidity, we recommend that all cases of Turner's syndrome should be carefully examined, and at the earliest suggestion of chronic or recurrent infection a full immunological assessment should be carried out.

- 1 Eisenstein EM, Sneller MC. Common variable immunodeficiency: diagnosis and management. *Ann Allerg* 1994;73:285-94.
- 2 Fischer MB, Hauber I, Eggenbauer H, Thon V, Vogel E, Schaffer E, et al. A defect in early phase of T-cell receptor mediated T-cell activation in patients with CVID. *Blood* 1994;84:4234-41.
- 3 Aukrust P, Lein E, Kristofferson AK. Persistent activation of TNF system in a subgroup of patients with CVI: possible immunological and clinical consequences. *Blood* 1996;87:676-86.
- 4 Baumert E, Wolff-Vorbeck G, Schlesier P, Peter HH. Immunophenotypic alterations in subsets of patients with CVI. *Clin Exp Immunol* 1992;90:25-30.
- 5 Cacciari E, Masi M, Fatini MP, Licastro F, Cicognani A, Pirazzoli P, et al. Serum immunoglobulin and lymphocyte sub-populations derangements in Turner's syndrome. *J Immunogenet* 1981;8:337-44.
- 6 Robson SC, Potter PC. Common variable immunodeficiency in association with Turner's syndrome. *J Clin Lab Immunol* 1990;32:143-6.
- 7 Wood CB, Martin W, Adinolfi M, Polani PE. Immunoglobulins and X-chromosome [letter]. *BMJ* 1969;4:110.
- 8 Rongen-Westerlaken C, Rijkers GT, Scholtens EJ, Van Es A, Wit JM, van den Brande JL, et al. Immunologic studies in Turner's syndrome before and during treatment with growth hormone. *J Pediatr* 1991;119:268-72.
- 9 Smith CIE, Vihinen M. Immunodeficiency databases—a new research tool. *Immunol Today* 1996;17:495-6.
- 10 Puck JM. Molecular basis for three X-linked immune disorders. *Hum Mol Genet* 1994;3(suppl):1457-61.
- 11 Kaczmarek RS, Webster ADB, Moxham T, Davison F, Sutherland S, Mufti GJ. CD4+ lymphocytopenia due to common variable immunodeficiency mimicking AIDS. *J Clin Pathol* 1994;47:364-6.
- 12 Spira TJ, Jones BM, Nicholson JKA, Lal RB, Rowe T, Mawle AC, et al. Idiopathic CD4+ T-lymphocytopenia—an analysis of five patients with unexplained opportunistic infection. *N Engl J Med* 1993;328:386-92.
- 13 Wright JJ, Wagner DK, Blaese RM, Hagenruber C, Waldmann TA, Fleisher TA, et al. Characterization of CVID: identification of a subset of patients with distinctive immunophenotypic and clinical feature. *Blood* 1990;76:2046-51.
- 14 Mahida YR, Gallagkar, Kurlak L, Hawkley CJ. Plasma and tissue IL-2 receptor level in inflammatory bowel disease. *Clin Exp Immunol* 1990;82:75-80.
- 15 Dennis NR, Collins AL, Corolla JA. Three patients with ring X chromosome and severe phenotype. *J Med Genet* 1993;30:482-6.
- 16 Collins AL, Cockwell AE, Jacobs PA, Dennis NR. A comparison of the clinical and cytogenetics findings in 9 patients with a ring (X) cell line and sixteen 45X patients. *J Med Genet* 1994;31:528-33.