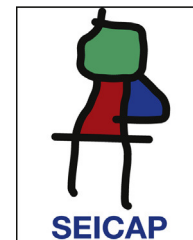




Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica,
Alergología y Asma Pediátrica

www.elsevier.es/ai



RESEARCH LETTERS

The diagnosis of common variable immunodeficiency in adults should not be missed: A delayed diagnosis can be devastating

To the Editor,

Common variable immunodeficiency is a heterogeneous disorder and one of the most common primary immune deficiencies (PIDs) in adults.^{1,2} Peaks of onset occur in early childhood and between the second and third decades of life.³ Recurrent upper and lower respiratory tract infections not responding to antibiotics and chronic diarrhoea are the main characteristics of common variable immunodeficiency (CVID).^{1–3} Especially, patients having a family history should be considered to be a possible CVID. The diagnosis of this disease depends on clinical and laboratory assessments.⁴ The diagnostic criteria for CVID were introduced by the European Society for Immunodeficiencies (ESID).⁵ According to these criteria, patients with CVID have a marked decrease of IgG and a marked decrease in at least one of the isotypes IgM or IgA (at least two standard deviations below the mean for age). In addition, CVID patients fulfil all of the following criteria: immunodeficiency begins at greater than two years of age, and poor antibody response to vaccines is observed. Intravenous immunoglobulin (IVIG) treatment at a dose of 400–600 mg/kg once every 3–4 weeks is essential for the treatment of patients with CVID.⁶ The serious and irreversible complications of CVID such as bronchiectasis and granulomatous disease involving many different organs can be prevented by IVIG treatment. In this report, we present two adult cases with PID in order to draw attention to these illnesses in adult patients.

Case 1, a 41-year-old male patient had been admitted to our emergency medical service with complaints of left lateral chest pain, shortness of breath and cough. On physical examination, his temperature 38.9°C, blood pressure 112/74 mmHg, pulse 98 beats/min, and respiratory rate 36 breaths/min had been found. He was alert and cooperative, but had pale skin. In thorax examination, decreased vibration by palpation, dullness by percussion, and absence of breath sounds by auscultation had been found on the baseline of left hemithorax. There were inspiratory fine crackles on both middle zones of hemithorax and lower zone of right hemithorax. The patient had been admitted to the intensive care unit of the pulmonary medicine clinic by making

a diagnosis of pneumonia and pleurisy by X-ray and computed tomography (Fig. 1). A chest tube had been placed for therapeutic and diagnostic aims. Clinical findings and laboratory data obtained by the examinations of specimens from the pleural fluid and needle biopsy had supported the diagnosis of empyema. Neither malignant cells nor microbial agents had been detected in the pleural fluid. Needle biopsy of the pleura had been reported as fibrinous pleuritis. The patient was referred to us three weeks after admission to pulmonary medicine clinic. The medical history of the patient revealed that he had been hospitalised due to four episodes of pneumonia and two episodes of meningitis in the last 15 years.

On admission, complete blood count (CBC) test showed leukocytosis ($12.4 \times 10^3/\text{mm}^3$; reference range [RR], $4\text{--}10.5 \times 10^3/\text{mm}^3$) dominated by granulocyte (88%; RR, 40–75%). He had increased erythrocyte sedimentation rate (ESR) (74 mm/h; RR, 0–15 mm/h) and C-reactive protein (CRP) (167 mg/L; RR, <8 mg/L) levels. The circulating levels of procalcitonin (PCT) (13.9 ng/mL; RR, <2 ng/mL) were consistent with bacterial aetiology. Serum protein electrophoresis was compatible with acute inflammatory pattern and hypogammaglobulinemia, since depressed albumin fraction (46.9%; RR, 52.0–67.0%) and prominent alpha-1 (16.4%; RR, 2.5–5.0%) and alpha-2 globulin fractions (18.9%; RR, 6.5–10.0%) and depressed gamma globulin fraction (1.8%; RR, 10.0–19.5) were seen. According to normal ranges for healthy population, the patient had lower levels of IgG (0.49 g/L; RR, 7–16 g/L) and IgA (<0.25 g/L; RR, 0.7–4 g/L), but normal levels of IgM (0.64 g/L; RR, 0.4–2.3 g/L). In lymphocyte subset analysis, the percentages of CD4⁺ T cells (17.6%; RR, 29–61%), CD19⁺ B cells (3.6%; RR, 6.4–23%), and total memory B cells (CD19⁺CD27⁺ B) (0.7%; RR, <11), were lower than those of normal ranges, while the percentage of CD8⁺ T cells (66.9%; RR, 11–38%) was higher than that of the normal range. In addition, the ratio of CD4⁺ T cells to CD8⁺ T cells (0.26; RR, 0.9–3.6) was found to be reduced in the flow cytometric analysis. Empirical antibiotic therapy had been started on admission and maintained throughout the hospital stay. As soon as the patient's symptoms and radiological signs improved (Fig. 1), the chest tube was removed within a week, and the patient was discharged with stable condition 35 days after hospitalisation.

Case 2, a 26-year-old female with lack of weight was referred by the gastroenterology clinic for immunological evaluation. She had chronic diarrhoea characterised by alternating stool consistency and frequency (7–8 times a

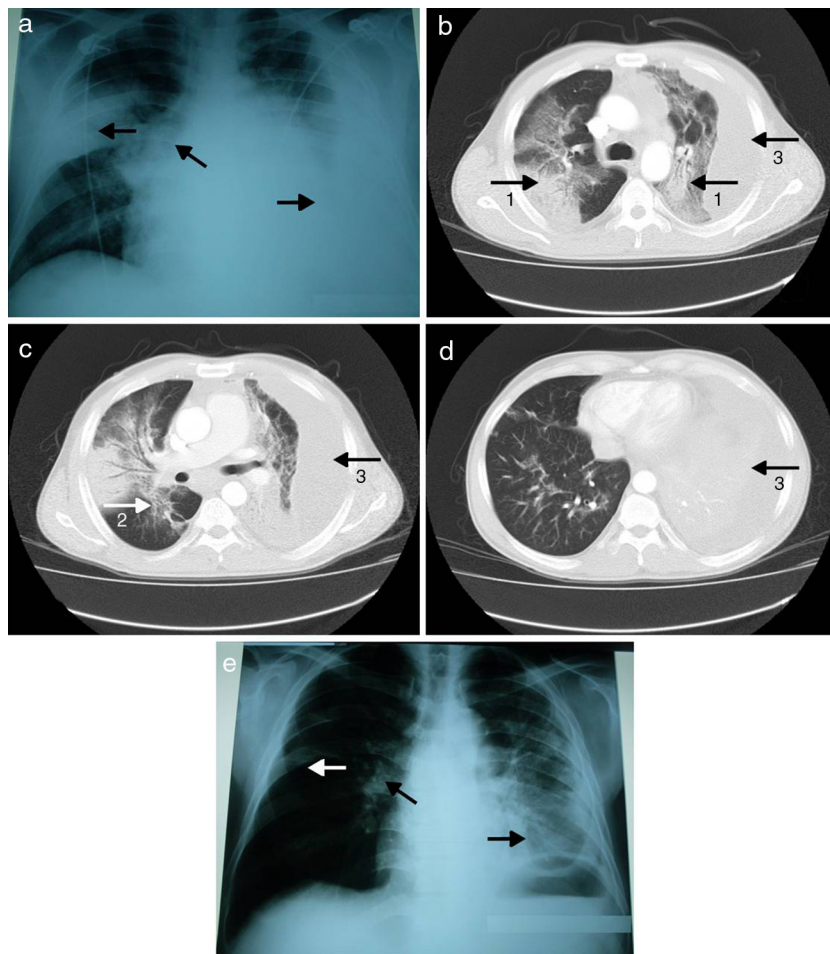


Figure 1 Chest X-ray and computed tomography images of patient 1. He had left-sided pleural effusion and right-sided pleura-based infiltration limited by fissure (arrows) on admission (a). Bilateral air bronchograms in infiltration areas (arrow 1 in b) and minimal bronchiectasis (arrow 2 in c) in upper and middle lobes of the right lung and lower lobe of the left lung and pleural effusion (arrow 3 in b, c and d) in the left hemithorax were detected by computed tomography. These radiological findings were resolved a week after the treatments with tube thoracostomy, empirical antibiotics and initial IVIG (e).

day) for the last 10 years. In childhood period, she had a history of recurrent upper respiratory infections. However, her main complaint was inability to have a child, although she had been married for four years and her menstrual cycle had been hormonally adequate. Besides the natural method, an attempt at in vitro fertilisation performed two years before had also failed. Because of this, her marriage was getting worse. On physical examination, her body mass index was lower than normal (15.42; RR, 18.5 to 24.99). Palpable and painless spleen and liver during inspiration and hyperactive bowel sounds were noted. The physical examination of other systems was within normal limits.

Microcytic hypochromic anaemia due to iron deficiency was observed in a CBC test (haemoglobin [Hgb]: 10.9 g/dL [RR, 11.7–15.5 g/dL], haematocrit [Hct]: 33.3% [RR, 34.5–46.3%], mean corpuscular volume [MCV]: 71.3 fL [RR, 80.4–95.9 fL], serum iron: 9 µg/dL [RR, 49–151 µg/dL], serum ferritin: 4.2 ng/mL [RR, 10–291 ng/mL]). She had increased ESR (38 mm/h; RR, 0–20 mm/h) and CRP (18 mg/L) levels. Serum protein electrophoresis showed a depressed gamma globulin fraction (3.9%) consistent with hypogammaglobulinemia and prominent alpha-1 (9.8%) and alpha-2

(12.6%) globulin fractions. Accordingly, the levels of IgG and IgA were lower than the normal ranges in repeated measurements (4.2 g/L and <0.25 g/L, respectively). The patient had reduced percentages of CD19⁺ B cells (1.2%) and total memory B cells (CD19⁺CD27⁺ B) (2.1%), and a decreased ratio of CD4⁺ T cells to CD8⁺ T cells (0.55) due to a reduced percentage of CD4⁺ T cells (28.1%) and an increased percentage of CD8⁺ T cells (50.8%). Mild gastritis and duodenal nodular lesions had been observed by gastroduodenoscopy, and multiple biopsy specimens had been taken from the duodenum. Nodular lymphoid hyperplasia, lack of plasma cells in lamina propria and *Giardia* had been reported in histopathological examination of biopsy specimens. Abdominal ultrasonography had revealed hepatomegaly (180 mm), splenomegaly (155 mm), enlarged para-aortic lymph nodes (the largest one 28 mm diameter), thickened mucosal folds consistent with mucosal oedema and increased peristalsis.

According to ESID criteria, these patients were diagnosed as common variable immunodeficiency (CVID). Thus, we started intravenous immunoglobulin (IVIG) treatment at a dose of 600 mg/kg, once every three to four weeks. Their complaints and clinical signs were dramatically improved

within three months of IVIG therapy. Patient 2 delivered a healthy term baby one year after IVIG therapy.

Atypical presentations of CVID such as autoimmune, allergic and malign disorders may be the first manifestation of patients other than infection.^{7,8} Therefore, these patients may be applied to various clinics, but remain undiagnosed because of the lack of awareness of these illnesses by medical professionals like practitioners and specialists other than immunologists.^{9,10} Accordingly, recurrent pneumonia, bronchitis, sinusitis or intractable diarrhoea in adults are mostly considered as an ordinary infection by the physicians. Both typical and atypical presentations of CVID were observed in our cases. We aimed to increase their serum IgG concentrations to 5–8 g/L by IVIG treatment, and dose adjustments were individualised according to clinical response and prevention of symptoms. With this report, we can learn some lessons from practice. Early and accurate diagnosis of CVID can improve the quality of life, reduce morbidity and mortality of patients, and prevent economic losses due to wrong treatments or treatments of its complications. The regular training programmes for medical professionals should be organised to keep their consciousness awake for CVID. The patients with suspected CVID should be evaluated by the clinical immunologists as soon as possible.

Ethical disclosures

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document.

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this investigation.

References

1. International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies. Notarangelo LD, Fischer A, Geha RS, Casanova JL, Chapel H, Conley ME, et al. Primary immunodeficiency diseases: 2009 update. *J Allergy Clin Immunol.* 2009;124:1161–78.
2. Llobet MP, Soler-Palacin P, Detkova D, Hernández M, Caragol I, Espanol T. Common variable immunodeficiency: 20-yr experience at a single centre. *Pediatr Allergy Immunol.* 2009;20:113–8.
3. Di Renzo M, Pasqui AL, Auteri A. Common variable immunodeficiency: a review. *Clin Exp Med.* 2004;3:211–7.
4. García JM, Gamboa P, de la Calle A, Hernández MD, Caballero MT, García BE, et al. Committee of Immunology of the Spanish Society of Allergology and Clinical Immunology. Diagnosis and management of immunodeficiencies in adults by allergologists. *J Investig Allergol Clin Immunol.* 2010;20:185–94.
5. Conley M, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies: representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). *Clin Immunol.* 1999;93:190–7.
6. Bayrakci B, Ersoy F, Sanal O, Kiliç S, Metin A, Tezcan I. The efficacy of immunoglobulin replacement therapy in the long-term follow-up of the B-cell deficiencies (XLA, HIM, CVID). *Türk J Pediatr.* 2005;47:239–46.
7. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. *Blood.* 2008;112:277–86.
8. Agondi RC, Barros MT, Rizzo LV, Kalil J, Giavina-Bianchi P. Allergic asthma in patients with common variable immunodeficiency. *Allergy.* 2010;65:510–5.
9. Waltenburg R, Kobrynski L, Reyes M, Bowen S, Khoury MJ. Primary immunodeficiency diseases: practice among primary care providers and awareness among the general public, United States, 2008. *Genet Med.* 2010;12:792–800.
10. Thickett KM, Kumararatne DS, Banerjee AK, Dudley R, Stableforth DE. Common variable immune deficiency: respiratory manifestations, pulmonary function and high-resolution CT scan findings. *QJM.* 2002;95:655–62.

S. Yesillik^a, U. Musabak^a, O. Sener^a, A. Baysan^a, E. Ucar^b, F. Demirel^{a,*}, Z. Polat^c

^a *Gulhane Military Medical Academy and Medical School, Department of Internal Medicine, Division of Immunology and Allergic Diseases, Ankara, Turkey*

^b *Gulhane Military Medical Academy and Medical School, Department of Pulmonary Medicine, Ankara, Turkey*

^c *Gulhane Military Medical Academy and Medical School, Department of Internal Medicine, Division of Gastroenterology, Ankara, Turkey*

* Corresponding author.

E-mail address: fedemirel@gata.edu.tr (F. Demirel).

<http://dx.doi.org/10.1016/j.aller.2013.05.007>