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Journal of Clinical Science & Translational Medicine
ISSN: 2993-8260

# Hodgkin Lymphoma in a Girl with Common Variable Immune Deficiency: A Case Report and Review of Literature

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**Case Report**

**Volume 5 Issue 1**

**Received Date:** August 07, 2023

**Published Date:** September 20, 2023

DOI: 10.23880/jcstm-16000121

## Abstract

Common variable immune deficiency (CVID) is among the most primary immune deficiency disorders with unknown etiology which mostly presents in adulthood; however, some patients might show their symptoms during childhood. CVID usually increases predisposition to malignancies. Lymphoproliferative malignancies such as lymphoma are the most incident malignancies among the patients; however, the prevalence of Hodgkin lymphoma (HL) is low among the patients and just a few cases of the disorder reported in children. A 13 year old girl admitted to our ward with bilateral cervical lymphadenopathy has emerged since 13 months ago without any associated symptoms. She was a known case of CVID diagnosed at 1 year of age and was under regularly treatment of monthly IVIG and prophylactic antibiotic since then. The diagnostic approach to her lymphadenopathy led to HL diagnosis and she has undergone the standard chemotherapy protocol for HL which took about 6 months without any radiotherapy and showed complete remission. After 6 years of standard follow ups, she is still in complete recovery. To our knowledge, this report seems to be the tenth case of HL emergence in patients diagnosed with CVID during their childhood and the second case of HL emergence despite regularly receiving of monthly IVIG. Low stage of her HL (2A) and favorable response to the chemotherapy with prolong remission might be explained by the regularly prescription of IVIG since early stages of life; albeit these conclusions need to be approved with further studies in the future cases.

**Keywords:** Hodgkin Lymphoma; Child; Common Variable Immunodeficiency; Lymphoma Malignancy; Primary Immune Deficiency

**Abbreviations:** CVID: Common Variable Immune Deficiency; HL: Hodgkin Lymphoma; NHL: Non Hodgkin Lymphomas; IVIG: Intra Venous Immune Globulin; LDH: Lactate Dehydrogenase; EBV: Epstein - Barr virus; CMV: Cytomegalovirus; IHC: Immunohistochemical; ESR: Erythrocyte Sedimentation Rate; PET: Positron Emission Tomography.

## Introduction

Common variable immune deficiency (CVID) is the most common symptomatic primary immune deficiency. It affects approximately 1 in 10,000–50,000 people [1-4]. CVID caused by a defect in B-cell maturation usually presents as a deficiency of serum immunoglobulins with unknown

etiology [2,5]. Although most cases of the disorder are sporadic, less than 20% of cases are hereditary ones with autosomal recessive inheritance more commonly occur than autosomal dominance inheritance [6,7]. The patients usually have increased predisposition to recurrent bacterial infections, granulomatous and/ or autoimmune diseases as well as malignancies [2]. The age of onset of CVID is not consistent, and the diagnosis is generally delayed [1,8,9]. Despite presenting in both children and adults, the diagnosis is usually made between 20 and 40 years of age [1,10]; however, up to 20% of cases may present before the age of 20 years [1]. Nowadays, the prevalence of malignancy has increased in CVID patients more than before partly due to recent advances in life span of the patients because of improvements in novel diagnostic and therapeutic approaches [11,12], despite the true mechanisms of malignancy emergence in these patients are not yet fully understood. According to different studies, the incidence of malignancy in CVID patients is around 1.5-20.7% and usually occurs during the 4th-7th decade of life [1,11,13-16]. It has been reported that the incidence of malignancy among CVID patients with the onset of symptoms below 16 years of age or higher is about 2.5% or 8.5% respectively [17]. It sounds like CVID patients have an increased cancer incidence for all sites combined mainly due to non-Hodgkin lymphomas (NHL) and gastric carcinoma [1,11-16,18,19]. Various reports revealed that the incidence of lymphoproliferative malignancies including NHL has increased almost 5-6 times in CVID patients compared to general population [13,16,20-22]. Even if NHL is the most frequent malignancy might occur in people with CVID [11,13,15,19,21-23], HL reported very rarely in this group of patients ( < 1%) [2,24]. Moreover, HL incidence in children with CVID is not clear yet.

## Case Presentation

A 13 year old girl presented to our department with bilateral cervical lymphadenopathy has emerged since 13 months ago. The diameter of some lymph nodes was more than 1.5 cm, their consistency was firm and they were non-tender. Her other physical examination results were unremarkable. She had no history of B symptoms such as fever, weight loss, night sweat, itching or fatigue during the period of disease. During the time of recent disease she had consumed different combinations of antibiotics with no improvement. Her past medical history included recurrent sinopulmonary infections and coughing since 6 months of age led to Common Variable Immune Deficiency (CVID) diagnosis at 1 year of age. Since then, she has received regularly Intra Venous Immune Globulin (IVIG) monthly plus daily inhalation of Salbutamol spray and taking amoxicillin as a prophylactic antibiotic. Her parents were not related. Her family history of immune deficiency or malignancy was negative. Her laboratory tests showed WBC count: 4500/ mm3 with 65% PMN, 30% lymphocytes, 3% Monocytes and 2% Eosinophils. Her hemoglobin and platelet count were 12.7 g/dl and 186000/ml respectively. Other investigations results included ESR: 2, CRP: negative, Direct Coombs: negative, Serum Ferritin: 41 µg/L (normal range: 41 – 400 µg/L), Folate level: 7.5 ng/mL (normal range: 2.7-17.0 ng/mL), Lactate Dehydrogenase (LDH): 546 U/L (normal range: <320 U/L), and Vitamin B 12 level: 1036 pg/mL (normal range: 160 - 950 pg/mL). Her serologic tests for Epstein-Barr virus (EBV) or Cytomegalovirus (CMV) IgM and IgG antibodies were negative respectively. We checked her various serum Immunoglobulin levels which all of them were very low at the time (IgM: <0.25 mg/dl, IgG: 5.6 mg/dl, IgA: < 0.3 mg/dl). Her serum Copper and B2 microglubulin levels were 103 mcg/dl (normal range: 62-140 mcg/dl) and 2.2 mcg/ml (normal range: 0.7-1.80 mcg/ml) respectively. Her Chest x-rays (PA and Lateral) were normal. Her neck soft tissue ultrasonography reported multiple bilateral oval and round shape hypo echoic lymph nodes localized in submandibular and superior jugular chain. The Maximum size of the lymph nodes was 38mm × 18mm. Neck CT Scan showed there were multiple homogenous lymphadenopathies in bilateral jugular chains and posterior triangles (right side more than left side) as well as left submandibular regions. Moreover, Adenoid tonsil was prominent with nasopharynx narrowing. Other regions' CT Scans included thoracic, abdominal and pelvic regions were normal. There was no involvement outside the lymph nodes (called extra nodal involvement).

A bilateral bone marrow aspiration and biopsy were performed which the pathologic tests of both of them were normal. A lymph node biopsy revealed classical Hodgkin lymphoma disease (HL) (lymphocyte-rich subtype). Immunohistochemical (IHC) results of the sample reported as follow: CD30: no reaction, CD15: no reaction, CD20: a nodular pattern of growth with a good number of B cells in the background, CD3: T cell Rosettes around Lymphocytic and Histiocytic cells were seen. Ultimately according to the mentioned findings the stage of patient's disease was 2A, favorable. Generally, this group includes HL that is only on one side of the diaphragm (above or below) and that doesn't have any unfavorable factors such as generalized or bulky lymphadenopathy, B symptoms, and abnormal Erythrocyte Sedimentation Rate (ESR). According to the diagnosis, a routine chemotherapy treatment protocol has begun for the patient. The protocol included a cycle of Adriamycin, Bleomycin, Vinblastine and Dacarbasine (ABVD) alternatively with a cycle of Cyclophosphamide, Vincristine, Procarbasine and Prednisolone (COPP); each cycle repeated for 3 times. The total period of her chemotherapy has taken 6 months. No radiation therapy was used. Afterwards, an evaluation included laboratory tests contain complete blood count (CBC), ESR, LDH, as well as chemistry panel (CHEM) contained serum Copper, Ferritin, B2 microglobulin,

Vitamin B12 and Folate level were performed in the patient which the results of all of them were normal. Moreover, surveillance imaging included chest radiography (CXR), neck ultrasonography, thoracic, abdominal and pelvic CT scans as well as total body positron emission tomography (PET) were ordered which all of them showed the patient was in complete remission. The patient was followed for 5 years by regularly visits each 3 months for the first 3 years, and each 6 months for the next 2 years. Each visits included history taking, clinical examination, and blood work including CBC, ESR, LDH, as well as CHEM. Radiographic tests were performed at each visit included CXR, computed tomography (CT) of thorax, abdomen and pelvis, and functional imaging including PET. Fortunately, the patient is on complete remission after 6 years of surveillance already.

## Discussion

In this case report, we introduced a girl with CVID diagnosed at 1 year of age presented with HL when she was 13 years old. There are some interesting points of view about the patient as follow: 1- Very early onset of CVID symptoms (6 months of age); 2- Early diagnosis of CVID (at 1 year of age); 3- Negative family history of CVID. 4- Regularly monthly receiving IVIG by the patient since the diagnosis; 4- Emergence of the malignancy before adulthood; 5- Occurrence of a rare type of malignancy (HL). According to the different articles accessed, the median age at onset of CVID symptoms before adulthood was 2.3-14.5 years (range: 6 months to 17 years) [19-25]. Therefore, the case's age of symptoms' onset was very similar to the lower limit of normal range of disease onset in childhood. Moreover, the median age at CVID diagnosis mentioned 6.7-19 years in various reports (range: 4 years to 20 years) [19-25]; as previously discussed the patient age at diagnosis (at 1 year of age) was far lower than the above lower limit range; It seems this discrepancy is due to a few years' delay generally happens in the diagnosis of CVID cases. A very noticeable finding in the case is emergence of malignancy despite regularly receiving of IVIG since the CVID diagnosis at one year of age. Regardless of various reports mentioned that 1.5-20.7% of CVID patients will be developed malignancy [12-13,20,26], most of them usually emerged during the $4^{th}$-$7^{th}$ decade of life, and just a few cases of malignancy occurred in these patients before adulthood [11,13,14,20]. Furthermore, the malignant neoplasm developed an average of 11.5 years (range, 6.5-20.2) after the diagnosis of CVID was made [1,11,27]. In our case, HL developed 12 years after CVID onset. Despite a few articles reported that malignancy might emerge in CVID patients during childhood period, most of these reports mentioned occurrence of NHL [11,13,14,19,20,26,28,29], and there are a few reports of occurrence of HL in these patients [30-37]. Overall, in literature we could find 9 cases of HL reported in patients with CVID onset in childhood. The characteristics of the patients, their CVID and HL have summarized in Table 1 [30-37].

| Number | Author (year) | Sex | Age of CVID Onset (year) | Age of CVID Diagnosis (year) | Age of HL Diagnosis (year) | Histopathology Type of HL | Outcome | Reference Number |
|---|---|---|---|---|---|---|---|---|
| 1 | Ellwood (2005) | Male | 3 | 4 | 30 | lymphocyte depleted | dead | [30] |
| 2 | Aghamohammadi (2007) | Male | 4 | 10 | 12 | * | dead | [31] |
| 3 | Aghamohammadi (2007) | Female | 5 | 11 | 16 | * | dead | [31] |
| 4 | Aydogan (2008) | Male | 3 | 9 | 18.5 | * | alive | [32] |
| 5 | Tacildyze (2014) | Female | ? | ? | 15 | * | alive | [33] |
| 6 | Karadogan (2014) | Female | 8 | 8 | 16 | lymphocyte depleted | alive | [34] |
| 7 | Tatci (2016) | Male | 4 | 7 | 7 | mixed cellularity | dead | [35] |
| 8 | Rael (2016) | Female | 11 | 18 | 25 | classic | alive | [36] |
| 9 | Ozdemir (2019) | Male | ? | 9 | 9 | * | alive | [37] |
| 10 | The Present case | Female | 0.5 | 1 | 13 | lymphocyte rich | alive | |

* Not mentioned in the reference

? Unknown data

**Table 1:** A review of the characteristics of the childhood CVID cases involved with Hodgkin Lymphoma (HL).

The least age for CVID onset or diagnosis among the cases was in our patient (6 months of age and 1 year of age respectively). Generally, the mean age of CVID onset, CVID diagnosis and HL diagnosis among cases were 5 years (Minimum: 6 months, Maximum: 11 years), 10 years (Minimum: 1 year, Maximum: 18 years) and 16 years (Minimum: 7 years, Maximum: 30 years) respectively. Overall, the cases occurred in males more than females (55% versus 45%), the age of CVID onset was below 12 years, the age of CVID diagnosis in almost all of the patients (8 cases, 90%) was less than 12 years of age, and the age of Hodgkin lymphoma emergence was more than 7 years of age in all the patients; 4 patients were dead at follow up (66%) because of infection or chemotherapy complications. Just in 4 patients histopathology type of Hodgkin lymphoma have mentioned in the references; According to this, it sounds that no specific histopathology type of Hodgkin lymphoma has emerged in CVID patients. In addition to our patient, only one patient [32] has received IVIG regularly since CVID diagnosis and despite this, both of them developed Hodgkin lymphoma. Therefore, it seems that regularly receiving IVIG after CVID diagnosis hasn't had any preventive role at least for preventing of Hodgkin Lymphoma, albeit the number of reported patients was very limited and this conclusion needs to be assessed in more cases.

## Conclusion

In conclusion, despite CVID is the most common primary immune deficiency disorder in humans, its onset in childhood is far less common in comparison to adulthood. Besides, increased predisposition to malignancies is not commonly presented as a disorder during childhood. The presented case showed the typical clinical findings of CVID since very early stages of life and fortunately, correctly diagnosed very early. Furthermore, she received prophylactic antibiotic and IVIG regularly since her diagnosis. The more striking features in this case were early age of CVID onset and diagnosis. Moreover, emergence of Hodgkin lymphoma regardless of regularly receiving IVIG, low stage of the HL and favorable response to the chemotherapy are other worthwhile points of view. In this article, we reviewed the characteristics of Hodgkin lymphoma presented in cases with CVID onset in childhood as well as characteristics of their CVID.

## Patient Consent for Publication

Written informed consent for publication of the case report and any accompanying images, without any potential identifying information, was provided by the parents of the patient.

## Conflicts of Interest

The author declares no conflict of interest.

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