

Case Report

T-cell lymphoma with von Hippel-Lindau disease: a rare case report and review of literature

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Abstract: von Hippel-Lindau disease (VHLD) comprises a series of complicated clinical manifestations. We hereby described a unique case of co-existing T-cell lymphoma (TCL) and confirmed VHLD. The symptoms in this 42-year-old male included fever and pancytopenia. Overall tests and examination made an infectious process unlikely. The results of bone marrow biopsy confirmed the diagnosis. The purposes we described this case were to probe into the relationship between TCL and VHLD, which was not mentioned in previously literature. Combination of clinical, radiological, immunophenotypic, pathological, and genetic data plays an important role in improving the rate of diagnosis, particularly in the challenge for diagnosis of T cell non-Hodgkin lymphoma.

Keywords: von Hippel-Lindau disease, T-cell lymphoma, hematological neoplasm

Introduction

von Hippel-Lindau disease (VHLD) is a heritable multisystem cancer syndrome that is related to a germline mutation of the VHL tumor suppressor gene on the short arm of chromosome 3 [1]. VHLD has an incidence of 1/36,000 to 1/53,000 newborns [2]. VHL patients are predisposed to develop lesions of the central nervous system (CNS) and viscera. CNS lesions include hemangioblastomas, the most common tumor in VHL, and endolymphatic sac tumors (ELSTs). Visceral manifestations include renal carcinomas and cysts, pancreatic neuroendocrine tumors and cysts, pheochromocytomas and cystadenomas of the reproductive adnexal organs [3]. But few report covered hematological disorders, especially T-cell lymphoma.

T-cell lymphoma represents a heterogeneous group of diseases with varied clinical features, prognosis and response to treatment [4]. Their incidence seems to have increased recently, also because of an improvement in diagnostic methods. Such conditions now account for approximately 20-30% in Asia [5-7] and 5-10% in Europe and North America [8] of all lymphoid

neoplasms. The low incidence of T-cell lymphoma poses real difficulties for a complete and correct assessment. The unspecified lymphomas represent a heterogeneous group, which requires additional studies to elucidate their biological and genetic bases, to separate them.

We reported an unusual case of T-cell lymphoma with von Hippel-Lindau disease. To our knowledge, it has not been reported before. It revealed the challenge and the important role of combination of clinical, radiological, immunophenotypic, pathological, and genetic technique in T-cell lymphoma diagnosis.

Case report

History and examination

A 42-year-old male South American was admitted to our ward for 6 weeks history of intermittent fever ranging from 38-39°C and pancytopenia, and 1 week history of sore throat associated with brown nasal discharge and abdominal pain. 6 days oral moxifloxacin was not working. 5 weeks before admission, cell morphology of bone marrow smear showed three series decreased, mature granulocyte proliferation and increasing rate of lymphocytes.

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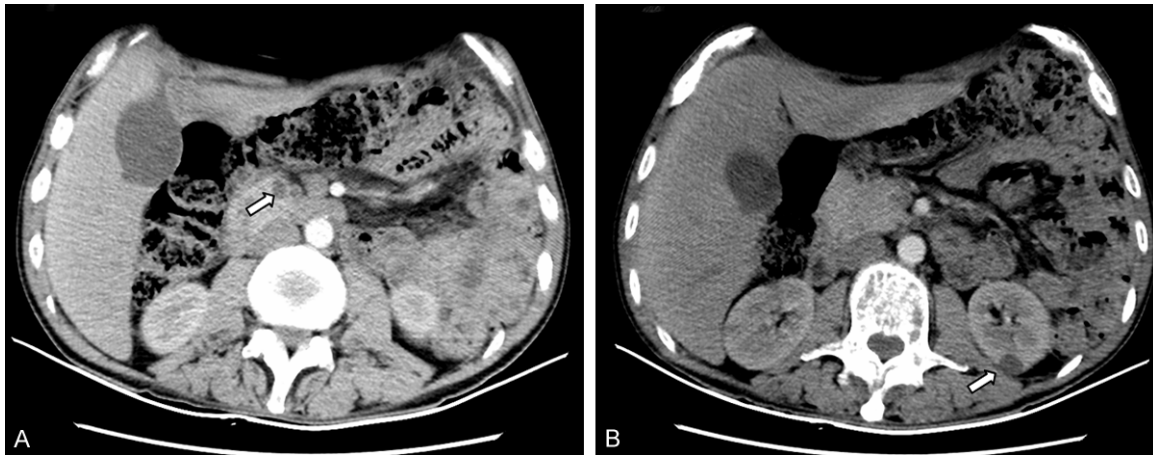


Figure 1. Radiologic characterization of VHL. A. CT imaging demonstrated multiple pancreatic cysts. B. CT imaging demonstrated multiple renal cysts.

Table 1. Immunophenotypic analysis by flow cytometer

Lymphocyte subsets (61.5%)	The expression rate (%)	Monocyte subsets (19.2%)	The expression rate (%)	Granulocyte subsets (10.0%)	The expression rate (%)
CD19+	2.4	CD4+	47.8	CD10+	/
CD20+	2.2	CD15+	36.8	CD15+	/
CD10+	0	CD11b+	95	CD11b+	/
CD38+	84	CD14+	78.2	CD16+	/
CD3+	58.1	CD13+	80.2	CD14+	/
CD3+CD4+	19.3	CD33+	79.6	CD33+	/
CD3+CD8+	24.7	HLA-DR+	78.8	CD13+	/
CD2+	91.1				
CD5+	53.3				
CD7+	89.9				

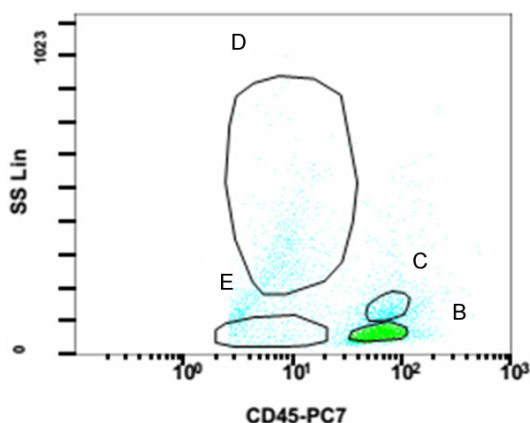


Figure 2. Immunophenotypic analysis by flow cytometer. CD45/SS scatter diagram showed normal CD45 subsets. B: Lymphocyte subsets (61.5%); C: Monocyte subsets (19.2%); D: Granulocyte subsets (10.0%); E: Erythrocyte subsets.

His past medical history included post thoracic hemangioblastomas resection and von Hippel-Lindau disease for 5 years confirmed by genetic test without family history.

On our physical examination, we just found pharyngeal hyperemia but no hepatosplenomegaly or superficial lymphadenopathy.

Hematologic examination still revealed pancytopenia. Negative blood and urine cultures, negative screening tests for EBV, CMV, HIV, HCV, T spot TB test, and normal transthoracic echocardiography made an infectious process unlikely. The rheumatologic markers, such as antinuclear antibodies (ANA), anti-extractable nuclear antigen (anti-ENA) and anti-neutrophil cytoplasmic antibody (ANCA) were negative. Tumor markers showed no abnormality except

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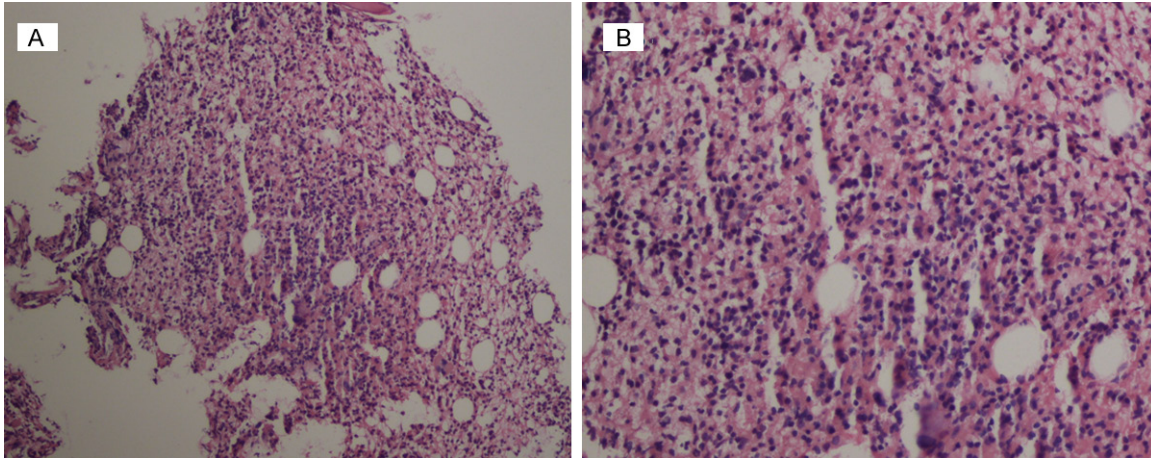


Figure 3. Histopathologic characterization of bone marrow biopsy. A. Histologic sections showed a little hemopoietic tissue and adipose tissue among bone trabeculae (H&E, 100 \times). B. A lot of abnormal hyperplastic cells with hyperchromatic nuclei appeared (H&E, 100 \times).

for mildly increases of neuron-specific enolase (NSE) and CyFRA211, and particularly markedly ascending thymidine kinase 1 (TK1). During the admission, ultrasound found some 6 \times 15 cm sized cervical lymph nodes which was located near bilateral vessels. An enhanced computed tomography (CT) of the abdomen showed multiple pancreatic cysts with calcification and renal cysts (**Figure 1**), and Chest CT revealed slight bilateral pneumonia. Nasal endoscopy, paranasal sinus CT and fundoscopy were normal.

Immunophenotypic and pathological findings

After 5-day treatment of Azithromycin and Ceftazidime, pharyngalgia and abdominal pain disappeared but hyperpyrexia, leukopenia and anemia were deteriorated. Thus, we repeated bone marrow puncture. Cell morphology analysis found 2% heterocysts with myeloid and erythroid series hypoplasia. The immunophenotypic results showed high ratio of lymphocyte subsets (61.5%) in bone marrow. The following markers were positive in lymphocytes: CD38, CD2, CD3, CD5, CD7 (**Table 1; Figure 2**). Pathological results of bone marrow biopsy reminded a lot of abnormal hyperplastic cells with hyperchromatic nuclei and a little hemopoietic tissue and adipose tissue among bone trabeculae. Marked pancytopenia was confirmed in hemopoietic tissue. Immunohistochemical staining demonstrated proliferating T lymphocytes positive reactivity for CD5+, CD7+ and CD3+, while no B lymphocyte hyper-

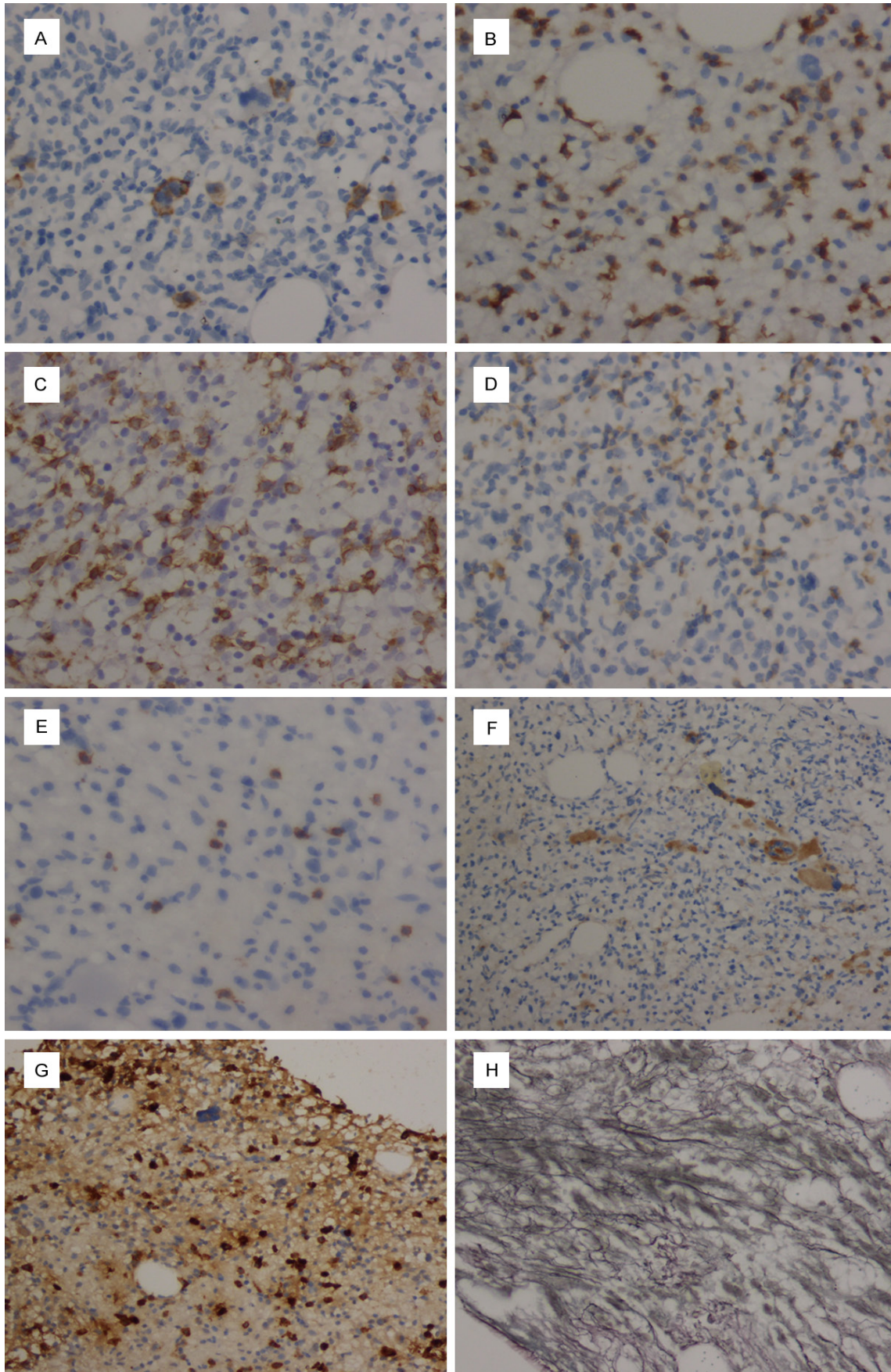
plasia, epithelial and neuroendocrine markers expression were found (**Figures 3, 4**). Immunohistochemical staining confirmed T lymphocyte neoplastichyperplasia.

The patient required to go back home for further treatment. So he was transferred to the local hospital and received chemotherapy after supportive treatment.

Discussion

VHLD is an autosomal dominant neoplasia syndrome, which was first described by the German ophthalmologist Eugene von Hippel and the Swedish pathologist Aavid Lindau at the beginning of the 20th century [3]. Its incidence is 1/36,000 to 1/53,000 of newborns [2]. VHLD is caused by a mutation in the VHL tumor suppressor gene on chromosome 3p25-26 resulting in the loss of the VHL protein (pVHL) tumor suppressor protein function [9, 10]. By the age of 65 years, more than 90% of individuals with VHL will display some disease related symptoms [11]. Patients with VHL are predisposed to develop specific central nervous system (CNS) and visceral lesions [1]. Affected individuals are at risk of developing various benign and malignant tumors of the CNS, kidneys, adrenal glands, pancreas, and reproductive adnexal organs. Because of the complexities associated with management of the various types of tumors in this disease, treatment is multidisciplinary. The following three criteria or genetic testing suggest a diagnosis of VHLD: (1) one or

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Figure 4. Immunohistochemical characterization of bone marrow biopsy. A. The CD30+ cells. B. The CD3+ cells. C. The CD7+ cells. D. The CD5+ cells. E. The CD20+ cells. (immunostaining, 400×). F. The CD31+ cells (megakaryocytic subsets). G. The MPO+ cells. H. The reticular fiber staining. (immunostaining, 100×).

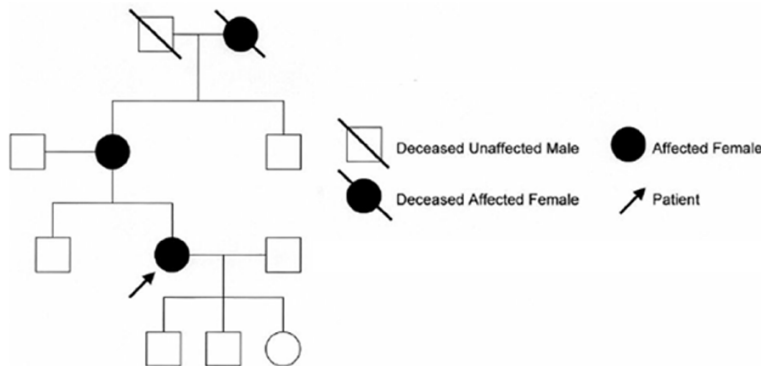


Figure 5. The pedigree of VHL.

more hemangioblastomas within the central nervous system (including retinal hemangioblastomas), typically in the cerebellum, (2) presence of visceral lesions (e.g. renal, pancreatic tumors/cysts), and (3) familial incidence (**Figure 5**) [12]. This patient was characterized by multiple tumors and cysts involved in spinal hemangioblastomas, pancreatic and renal cysts, as well as gene test, which was in accordance with VHL criteria.

The VHL gene is widely expressed in tissues, including those not affected by VHL. Post-translation, pVHL complexes elongin B, elongin C, Rbx 1 and Cullin 2 to form an ubiquitin ligase that proteolyzes the alpha-subunit of hypoxia-inducible factor (HIF), which coordinates cellular response to hypoxia through transcriptional regulation. HIF enhances glucose uptake and increases the expression of angiogenic, growth and mitogenic factors including, vascular endothelial growth factor (VEGF), platelet derived growth factor-beta chain (PDGF-B), erythropoietin and transforming growth factor (TGF) [1, 13]. With absent or abnormal pVHL function, HIF may constitutively stimulate angiogenesis and carcinogenesis by VEG, PDGF-B and TGF- α [14-16]. Besides being a potent mitogenic factor, TGF- α stimulates cellular over-expression of the epidermal growth factor receptors (EGFR, the receptors for TGF- α) creating a potential autocrine loop [15]. Dysfunction of VHL-HIF axis is the one of reasons of VHL-related carcinogenesis. But rare case reports hematological neoplasm with VHL. We just

reviewed a case report in Hodgkin's disease [17], but no TCL. Thus, we described the special case of co-existing TCL and VHL.

T-cell lymphomas represent a heterogeneous group of diseases with varied clinical features, prognosis and response to treatment. There are 22 different types of T-cell and NK-cell lymphomas according to WHO Classification [18, 19].

Predominantly nodal lymphoma subtypes include angioimmunoblastic T-cell lymphoma (AITL), anaplastic large-cell lymphoma (ALCL) anaplastic lymphoma kinase (ALK)-positive, anaplastic large cell lymphoma (ALCL) ALK-negative (provisional entity) and peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). Predominantly extranodal lymphoma include extranodal NK/T-cell lymphoma nasal type, enteropathy-associated T-cell lymphoma (EATL), hepatosplenic T-cell lymphoma (HSTL), subcutaneous panniculitis-like T-cell lymphoma-alpha beta (SPTCL). Mature T-cell leukaemias include T-cell prolymphocytic leukaemia (T-PLL), T-cell large granular lymphocyte leukaemia (T-LGL), aggressive NKcell leukaemia, chronic lymphoproliferative disorder of NK-cell (provisional entity), adult T cell leukemia/lymphoma-HTLV positive (ATLL), systemic EBV positive T-cell lymphoproliferative disease of childhood, hydroa vacciniforme-like lymphoma. Cutaneous predominant subtypes include Mycosis fungoides (MF), Sezary syndrome (SS), primary cutaneous CD30-positive T-cell lymphoproliferative disorders (lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma), primary cutaneous gamma-delta T cell lymphoma, primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma (provisional entity), primary cutaneous CD4 positive small/medium T-cell lymphoma (provisional entity). The diagnosis of T cell lymphomas is very laborious. Clinical, immunophenotypic, histopathological, immunohistochemical, molecular and genetic find-

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ings must be correlated as none of them is strong enough to be used alone for diagnosis. In our case, we cannot make sure the exact classification of T-cell lymphoma. But based on the specific markers for T lineage (CD2+ CD5+ CD7+ CD3+low CD4+), T lymphocyte neoplastic hyperplasia was confirmed. Combined with histopathological, immunohistochemical findings in bone marrow, the specific markers for T lineage (CD5+ CD7+ CD3+) verified that the dysplastic cells were T lymphocyte.

We reported this case in order to emphasize the great real difficulties for a complete and correct assessment. The group of TCL remains a challenge for researchers. It is important to diagnose TCL by clinical, radiological, immunophenotypic, pathological, and genetic examination. It is helpful to improve the rate of diagnosis. To date no report showed TCL with VHL. So it is the other aim of this report to study the connection of TCL and VHL. Some previous researches show partly hematological neoplasm is related to the epigenetic changes of VHL [20, 21]. Gene transfer of VHL inhibits the growth of transplanted EL-4 lymphoma cells and the HIF1 inhibitor suppresses leukaemia cell growth in association with reduced NOTCH1 expression [22, 23]. But the definite mechanism is not clear now, and further research is necessary.

Conclusions

In conclusion, we reported a case of a patient with co-existing TCL and VHL. We hope that the study would help to make correct diagnosis for TCL in the future and contribute to a better understanding in the relation of TCL and VHL.

Disclosure of conflict of interest

None.

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