A case report of lymphoid intestinal pneumonia in common variable immunodeficiency

Oligoclonal expansion of effector lymphocytes with preferential cytomegalovirus-specific immune response and lymphoproliferative disease promotion

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Abstract

Rationale: Lymphoid interstitial pneumonia (LIP) is a rare disease with lymphocytic infiltration of the alveolar interstitial and air spaces, sometimes classified as a clonal lymphoproliferative disease (LPD) with high prevalence in patients with immunodysregulation. Although association of mucosa-associated lymphoid tissue (MALT) lymphoma development with infectious agents has been well described, it is not so in the case of LIP. Attempts to demonstrate an infective cause by direct microbe detection have failed, but association with atypical specific immune response to opportunistic infectious agent has not been studied.

Patient concerns and Diagnoses: We performed clinical, biochemical, and immunologic analysis of patients LIP that arises primarily from the common variable immune deficiency (CVID) with normal immunoglobulin class M (IgM) level and mild infectious course as a result of immunodysregulation. At the age of 13 multiple nodules, areas of consolidation were observed and LIP was confirmed by histological examination. The progression of the disease with massive splenomegaly (17 → 27 cm), lymphadenopathy soft tissue infiltration coincides with high standardized uptake value (SUV was 3.1–5.2), regulatory T cells decrease (CD4 +25% FoxP3+ level – 0.02%, i.e., 8 cells per 100 μL), oligoclonal gammopathy: very high IgM (3340 mg/dL) and β2-microglobulin (18.8 mg/L) level observed 10 years later.

Immune response polarization was observed in humoral and cellular compartment -Th and Tc-dependent: 10.8% of lymphocytes are CD8high+CMV pp65-pentamer positive cells (Epstein–Barr virus-specific not observed). Specific immune response polarization correlates with negative immunofixation, light chains κ/λ = 2.84 and narrow, but non-monoclonal T cell receptor (TCR)/ B cell receptor (BCR) repertoire.

Lessons: Taking everything into account, this case report shows that LIP is a consequence of immune-dysregulation in CVID, that is, Treg deficiency, narrow lymphocyte repertoire, and abnormal ability to respond to cytomegalovirus (CMV) antigens. It may be visualized by positron emission tomography (PET) and monitored by CMV-specific immune response, β2-microglobulin level, and IgM paraproteinaemia, but not by immunofixation and κ/λ ratio.

Abbreviations: BAL = bronchoalveolar lavage, BALT = bronchus-associated lymphoid tissue, BCR = B cell receptor, CVID = common variable immunodeficiency, FDG = fluorine-18 fluoro-deoxyglucose, LIP = lymphophillitivious lymphoma/pneumonitis, LPD = lymphoproliferative disease, MALT = mucosa-associated lymphoid tissue, PET = positron emission tomography, SUV = standardized uptake value, TCR = T cell receptor, Treg = regulatory T cells.

Keywords: β2-microglobulin, BCR TCR repertoire, bronchus-associated lymphoid tissue, common variable immune deficiency, cytomegalovirus, IgM paraproteinaemia, lymphoid interstitial pneumonia, lymphoma, positron emission tomography, regulatory T cells

1. Introduction

Lymphoid interstitial pneumonia/pneumonitis (LIP) is a rare disease with lymphocytic infiltration of the alveolar interstitium and air spaces and sometimes classified as a lymphoproliferative disorder (LPD).[1,2] Although statistical LIP and common variable immune deficiency (CVID) coexistence is evident[3] (LIP appears in 3% of CVID patients),[4] the descriptions of strict pathomechanism that prompts lymphocytic infiltration and granuloma formation are ambiguous. Furthermore, the molecular gene rearrangement is occasionally tested.[5] The radiologic findings of the primary lymphoid lesions are often nonspecific and, contrary to lymphomatoid granulomatosis, positron emission tomography (PET) is not used as a diagnostic tool.[1,6,7] One case report of increased metabolic activity at PET is found in LIP—in nodules that are larger than 11 mm.[8]
This case report shows immunodysregulation, CMV-specific T and B cells immune response polarity, and LIP development in CVID patient, but without viral replication.

Patient gave informed consent for the sample analysis in accordance with the 5 Declaration of Helsinki.

2. Case presentation

A CVID-diagnosed, 15 years old girl developed LD: initially the hipogammaglobulinemia, warm autoimmune-hemolytic anemia was observed. CD19+B cell count was quite normal, CD40/CD40L mutation and X-linked or secondary agammaglobulinemia were excluded. Contrary to activation-induced cytokine deaminate deficiency lymphadenopathy with lymphoid hyperplasia and giant germinal centers are not observed. Late onset corresponded with mild infectious complications. Opportunistic infection such as pneumocystis, streptococcus, and other encapsulated bacteria did not occur. CVID diagnosis was consistent with ESID criteria. It is noteworthy that slight increase of initial immunoglobulin class M (IgM) level corresponded with positive results of anti-CMV, -herpes simplex virus, -Epstein–Barr virus [EBV], -varicella zoster virus IgM antibodies (Table 1).

Three years later the restrictive, granulomatous lung disease developed: open lung biopsy and histological examination showed lymphocytic infiltration of interstitial tissue: LIP diagnosis was confirmed. Analysis of fluid obtained by bronchoalveolar lavage (BAL) showed an increase in the total cell count, predominantly in lymphocytes and neutrophils. BAL, blood, urine, bone marrow, sputum cultures were all free of bacteria, mycobacteria, actinobacteria, and fungi (especially tuberculosis, Nocardia, Actinomyces, Pneumocystis, Aspergillus spp). CMV, EBV, HHV6, HIV, hepatitis C virus polymerase chain reaction (PCR) analyses were also negative.

2.1. Course and clinical findings

Massive splenomegaly, oligoclonal gammopathy: very high IgM level (3840 mg/dL), cold agglutinin disease, cryoglobulinemia, serum sickness-like reaction with hyperviscosity were observed 10 years later (Table 1); Waldenstrom macroglobulinemia-like clinical symptoms (e.g., hyperviscosity) and hipergamaglobulinemia with very dense band in serum electrophoresis (Fig. 1B) were observed, but without monoclonal antibody in immunofixation (not shown, λ/κ = 2.84). It corresponded with severe exacerbation of pulmonary symptoms, infiltration with lymphoplasmycatic cells in peripheral tissue and decrease of regulatory T cells (CD4+CD25+FoxP3+ Treg <1 cell/μL) (Table 2). Immunohistochemical and flow cytometry analysis showed infiltrating CD20+138+ plasmacytoid cells, Ki-67 ~50%, lack of EBV antigen (LMP-1), and CMV/EBV-DNA. In blood B cells are surface immunoglobulin negative (Table 2). The aforementioned tests for infectious agents were still negative. Although we detected CMV neither in the blood nor in other specimens (BAL) by PCR, the vigorous cellular (gamma interferon release, CMV-pentamer positive CD8 cells) and humoral (class IgM) immune response were observed. Glucocorticoid and ganciclovir therapy was ineffective. PET showed high uptake of 18F-Fluorodeoxyglucose ([18F-FDG]) in pulmonary granulomas and spleen: standardized uptake value (SUV) was 5.31 to 5.47, respectively (Fig. 1C). To assess abnormal T and B receptor repertoire (as guidelines to understanding specific lymphocyte polarization) the multiplex PCR assays have been used for the detection of clonally rearranged immunoglobulin (BCR) and T cell receptor (TCR) genes as described elsewhere. In spite of normal numbers of peripheral T and B cells, complementary determining region analysis of T cell receptor (TCR) and immunoglobulin heavy chain showed restricted repertoire (Fig. 1A). Other immunological data are summarized in Tables 1 and 2.

3. Discussion

Despite the fact that some of B cells have passed through the germinal center and sometimes antigen-specific IgM production is observed, the TCR clonality analysis shows that T cells abnormality may be fundamental. Bronchus-associated lymphoid tissue (BALT) is not present at birth, develops in childhood, and is again absent in the normal healthy adult. BALT—a type of Mucosa-associated lymphoid tissue (MALT) lymphoproliferative disease is a result of chronic stimulation: BALT reappears in adults with antigenic stimulation, such as

| Parameter | Initial value | Exacerbation (10 y later) | NORM |
|-----------|---------------|--------------------------|------|
| Splen size, cm | 17 | 19 × 12 × 26 | 16 |
| Lymphadenopathy | Mild | Regional | |
| B2−microglobulin, mg/L | 5.31 | 18.80 | 0.70–1.80 |
| Total bilirubin, mg/dL | 0.47 | 1.8 | 0.20–1.30 |
| Haptoglobin | 85 | Not detected | 30.0–200.0 |
| Complement C3c, mg/dL | 118 | 27 | 90–180 |
| Complement C4, mg/dL | 14.20 | 4.20 | 10–40 |
| Humoral | | | |
| IgG, mg/dL | 39 | 500–900 (IVIG) | 700–1600 |
| IgA, mg/dL | <24 | <24 | 88–410 |
| IgM, mg/dL | 333 | 3810 | 34–210 |
| IgE, μL/mL | <17.7 | <17.7 | |
| Light chains κ | 300 | 506.0 mg/dL | 170–370 |
| Light chains λ | 145 | 178.0 mg/dL | 90–210 |
| κ/λ | 2.06 | 2.84 | 1.35–2.65 |
| Immunofixation | Negative | Negative | |
| Specific antibody [NTU]∗ | | | |
| CMV IgM | +[25.23] | +[54.20] | |
| CMV IgG | −[0.86] | NA | |
| EBV IgM | +[21.59] | −[0.55] | |
| EBV IgG | −[0.46] | NA | |
| HSV IgM | +[23.93] | −[0.55] | |
| HSV IgG | −[0.34] | NA | |
| VZV IgM | +[14.59] | Equivocal [1.05] | |
| VZV IgG | −[0.46] | NA | |
| Cold agglutinin | NT | Strong positive | |
| Warm agglutinin | NT | Negative | |
| Cellular (i.e., quantiferon)δ | | | |
| CMV-specific epitopic peptides | 9.06 IU/mL | | |
| Control | 0.66 IU/mL | | |
| PHA | 4.00 IU/mL | | |

Initial mild interstitial pneumonia corresponded with significant increase of β2-microglobulin, but slight increase of spleen size and IgM level without C3c and C4 complement decrease. Specific IgM was observed to all herpes viruses. During exacerbation high IgM with complement consumption strong lymphocyte polarization was observed: in humoral (positive CMV-specific IgM only) and cellular compartment. Viropro CMV-specific interferon γ release was higher than nitrogen-induced i.e., phytohaemagglutinin PHA-induced. Immunoglobulin’s levels were determined by turbidimetry (Olympus).

CMV = cytomegalovirus, EBV = Epstein–Barr virus, IgA = immunoglobulin class A, IgD = immunoglobulin class D, IgE = immunoglobulin class E, IgG = immunoglobulin class G, IgM = immunoglobulin class M, HSV = herpes simplex virus, NT = not tested, VZV = varicella zoster virus.

† NTU—nephelometric turbidity units (NTU).

‡ Quantiferon—gamma interferon-releasing assay.
Table 2

Cytometry analysis.

| Population of lymphocytes | Initial value | Exacerbation (10 y later) |
|---------------------------|---------------|---------------------------|
| Lymphocytes total value, cells/μL | 1109 | 1130 |
| Specific CD8+ T cells | | |
| EBV-BMLF1-13pentamer+ cells† | n.t. | 0.02% (22.6/100μL) |
| EBV-LMP1pentamer+ cells‡ | n.t. | 0.05% (55.5/100μL) |
| CD8high+ CMVpp65-pentamer+ cells* | n.t. | 10.9% (123/μL) |
| Regulatory T cells (Treg) | | |
| CD3+CD4+CD25+ | % (cells/μL) | 0.4% (104/μL) | 0.54% (6/μL) |
| CD3+CD4+CD25high+ | % (cells/100μL) | 0.2% (221/100μL) | 0.02% (22.6/100μL) |
| FoxP3+CD4+CD25high | % (cells/100μL) | n.t. | 0.01% (11.3/100μL) |
| B cells | | |
| CD19+ | % (cells/μL) | 4.7% (53/μL) | |
| CD19+K+ | % (cells/100μL) | 0.07% (79.1/100μL) | |
| CD19+L+ | % (cells/100μL) | 0.05% (55.5/100μL) | |

Although lymphocyte level was stable, the significant decrease of CD4+CD25high regulatory T cells level was observed. Specific CD8 cells were tested for specificity using pentamer technique: there was a very low level of CD8 T cells that respond to EBV. On the contrary, vigorous CD8 response to CMV antigens was observed. In lymphoproliferative exacerbation (Table 2), (B) in humoral compartment serum sickness and very high level of nonmonoclonal IgM paraproteinemia with complement consumption were observed. A very dense band in the γ-globulin region of the serum proteins appears polyclonal because of its size in width and great density. Although immunofixation was negative and light chains k/λ ratio was insignificant (2.84), TCR/EBV oligoclonal (see, A) — the clinical manifestation and hyperviscosity resembles malignant lymphoproliferative disease (Waldenstrom macroglobulinemia, lymphoma). (C) Positron emission tomography (PET) during progression of the lymphoproliferative disease. Highest uptake of 11C-fluoro-deoxyglucose was seen in pulmonary granulomas with lymphoid tissue (standardized uptake value [SUV] was 3.1–5.2). It corresponded with histological findings: high proliferative response (Ki67 — 50%), lymphoplasmacytoid CD20+CD138+ B cells infiltration and high β2-microglobulin level, known prognostic marker for lymphoproliferative diseases. CMV — cytomegalovirus; CVID — common variable immunodeficiency, IgM — immunoglobulin class M.
infection, cigarette smoking, chronic inflammation, but the specific antigens are rarely identified, usually diagnosed without gene arrangement analysis.\[3,5,12\]

It is a general paradigm that in most patients with suspected LPD, immunohistology or cytometry can discriminate between malignant and benign/reactive.\[24\] On the contrary, in cases of abnormal TCR/immunoglobulin gene rearrangement in CVID,\[11\] observed here, making the diagnosis is less evident. Differentiation between LIP and pulmonary MALT/BALT lymphoma is not clear-cut.\[5,12\] The distinct entities in accordance with the WHO classification unfortunately arise in mucosal sites where the lymphocytes are not normally present and non-self antigenic stimulation is high. Waldenstrom macroglobulinemia-like phenomena and tomographic/PET findings were observed here but without signs of humoral/cellular clonality and clear malignancy (immunofixation was negative, \(\alpha/\beta\), not significant, and IgH-not clonally rearranged Fig. 1).\[1,24\] The role of infectious agents in such situation is probably underestimated due to rare use of PET, PCR, and pentamer technique and TCR/BCR repertoire analysis as preemptive diagnostic tools. Due to marginal zone origin MALT lymphoma B-cells have somatically mutated IgHV genes in all cases. On the other hand, microbial stimulation and antigenic pressure suggest that the lymphoid cells undergo antigen selection and that their expansion remains antigen-driven (gastric MALT lymphoma shows complete response after antibiotic therapy).\[2,12\] Antigen-specific immune response, T and B-cell proliferation is usually non-monoclonal: infectious agent contains many multiepitopic proteins. It is noteworthy that CMV-specific epitopes used in pentamer and QuantiFeron (gamma interferon release after antigen stimulation) techniques are distinct. Therefore, it confirms oligoclonal CMV-specific T cell receptor repertoire. Lymphopenia in CVID, low cellularity, small biopsy specimen in the diagnosis of LIP and extranodal MALT lymphoma may be the source of false results of clonality.\[13\] Furthermore, in one study, the rearrangement was detected in half of the cases, which changed the diagnosis from LIP to lymphoma in spite of histomorphology, clinical manifestation, etc.\[1,11\]

4. LIP pathogenesis

The etiology of LIP remains obscure: attempts to demonstrate direct infective cause by PCR, viral antigen staining, or in situ hybridization have failed.\[4\] On the other hand, initial serum IgM levels are one and only important factor in the prognosis of CVID, since there is a significant correlation between increased IgM and the development of polyclonal lymphocytic infiltration (\(P = 0.018\)) or lymphoid malignancy (\(P = 0.02\)).\[14\] In the case of microvascular abnormality, IgM paraproteinaemia precedes and probably prompts lymphocytes infiltration, then granuloma formation. It is observed, for example, in a Sjögren syndrome and Wegener granulomatosis with non-monoclonal granulomatous lung disease (GLILD).\[15\] IgM are pentameric in structure, induce more aggressive complement activation than immunoglobulin class G. Classical complement cascade activation by CMV-specific IgM, but also alternative by pentameric IgM, may be pathomechanism of serum sickness, observed here C4 and C3 decrease and hemolysis with haptoglobin consumption (Table 1). The commonest autoimmune conditions in CVID are the cytopenias (immune thrombocytopenia, hemolytic anemia) that occur in 11% to 12% of patients.\[14\] Due to its potentially destructive nature for host tissues complement activation contributes also to LIP pathogenesis. Decrease of complement level (Table 1), its role in the elimination of circulating immune complexes is cause of prolong circulation of such complexes and observed here serum sickness symptoms. Further, complement-and CMV-induced IFN-\(\gamma\) secretion (Table 1) result in the protease release: critical factor for remodeling of damaged tissue.\[15\] It is a well-known pathway in LIP as a pulmonary complication of systemic lupus,\[15,25\] but in CVID—not.

The mechanism proposed to underline the autoimmune phenotypes in CVID includes low Treg level.\[15\] We observe the low level of FoxP3+Tregs (\(\leq 1\) cell/\(\mu L\) see Table 2) during fast LPD progression: last evidence points out that Tregs not only inhibit tumor-specific T cells but may also have a role in suppressing the progression of the B-cell tumor.\[16\] Defects in recombination activation gene (RAG 1/2) have been shown to lead to abnormal B (BCR) and T cell receptor (TCR) repertoires that are an accurate diagnostic tool and heuristic guideline to understanding pathophysiology of immunodeficiency. Last findings show constricted T cells repertoire in CVID (to some degree observed here), but unfortunately without specific clinical complications.\[15\] Therefore, this is the first report on abnormal and reduced TCR and especially BCR diversity as a cause of immunodysregulation in CVID with LPD development. BALT is not present at birth, develops in infants and young children, and is again absent in the normal healthy adult, but reappears in adults with antigenic stimulation.\[16\] CMV-specific IgM response has not been so far described in LIP; we also observe vigorous CMV-specific IFN-\(\gamma\) T cell response and high expansion of CMV-specific effector CD8(+) T-cell subset (Tables 1 and 2). The increase of CMV-specific IgM observed during exacerbation and disappearance of others indicates indirect role of CMV in immunodysregulation. Last experimental study shows subset of CVID patients that have debilitating inflammatory complications strongly associated with cytomegalovirus infection and a hyperproliferative CMV-specific CD8+T-cell response.\[17\] Within the CMV-specific population, the frequency of late effector cells correlates inversely with the frequency of cells expressing programmed death 1\[1,17\] and, therefore, are resistant to apoptosis, crucial immunoregulatory mechanism. In our patients CMV-induced secretory and hyperproliferative immune response of CD8+T cells was evident (see Tables 1 and 2—quantiferon and pentamer analysis). It corresponded with LPD exacerbation, high level of \(\beta\)2-microglobulin (HLA class I light-chain, expressed on all nucleated cells and released in viral infection after cytopotoxic immune response or during LPD), but PCR analysis did not confirm active CMV replication in blood nor BAL samples. The use of fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography scan (PET) as a diagnostic tool in gastric MALT is well described, but its sensitivity in extragastric localizations is sometimes better.\[12\] MALT lymphoma lesions after antigenic stimulation are hypermetabolic at PET\[18\] and in our case high SUV corresponded with strong BALT activation, CD20+138+ plasmacytoid cells infiltration with high proliferative response (Ki-67 – 50%) (Fig. 1C). Further, FDG uptake in post-transplant lymphoproliferative disease (PTLD) lesions is useful in defining the extent of the disease.\[3\] Such approach prompts the use of PET as a diagnostic tool in LIP and other LPDs (benign or malignant) in CVID for the evaluation of the disease range, for disease monitoring or if the localization of most intensive inflammatory foci is crucial (e.g., for representative biopsy, BAL, PCR analysis of infectious agent). An initial PET may detect additional sites of disease and indicate its intensity (Fig. 1C).

Therefore, Treg level, CMV-specific immune response, IgM paraproteinaemia with complement consumption, SUV, and \(\beta\)-
The microglobulin level may be used as leading parameters of LIP (i.e., corresponding with Ki-67 and histological findings), but markers of clonality: clonal IgH rearrangement, immunofixation, and κ/λ ratio or other signs of malignancy (e.g., preferential κ or λ-positive B cells propagation)—unfortunately not (Fig. 1, Tables 1 and 2).[9,13] This study has obvious limitations because of casuistic nature, but timeline (specific dates) study of larger scale is difficult. Furthermore, the qualitative dimension of lymphocyte repertoire is at least as important as the quantitative one.

5. Conclusions

Treg decrease, narrow lymphocyte repertoire observed in CVID and strong specific stimulation by prevalent antigen such as CMV prompt BALT reappearance, LIP, and lymphoproliferative disease development by immunodysregulation: hyperproliferative CMV-specific T-cell response, vigorous IFNγ, and IgM secretion (Fig. 2). The predictive value of SUV intensity, Treg and anti-CMV immune response, IgM paraproteinaemia, β2-microglobulin is higher than immunofixation, serum κ/λ ratio, and predominance of κ- or λ-positive B cells.

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