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Case Report

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Case report on a rare pulmonary bacterial infection by Actinomyces odontolyticus in a T-cell large granular lymphocyte leukemia patient

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Abstract

T-cell large granular lymphocyte leukemia (T-LGLL), a rare and indolent chronic lymphoproliferative disorder, represents 2% to 3% of chronic lymphoid leukemia cases and affects equally male and female around 60 years. It is characterized by neutropenia that can be severe and lead to opportunistic infections. We report here the case of a 67-year old woman that was followed for T-LGLL, who was diagnosed with lung infection due to *Actinomyces odontolyticus*, a gram positive bacillus and less commonly recognized pathogen of the Actinomyces group. The diagnosis was based on clinical (dry cough, alteration of general state, dyspnoea), CT-scan and microbiologic features. The treatment consisted of high and intensive dose of beta-lactamine over a 6-month long period combined with once or twice-weekly injections of G-CSF. Treatment with cyclophosphamide intended at raising neutrophil count ≥1000/mm^3 has been successfully implemented.

Keywords: T-cell large granular lymphocyte leukemia, neutropenia, Actinomyces odontolyticus.

INTRODUCTION

T-cell large granular lymphocyte leukemia (T-LGLL) is a spectrum of rare, chronic and indolent lymphoproliferative disorders defined by clonal amplification of either CD3+ cytotoxic T-lymphocytes or CD3- natural killer (NK) cells as described in 1975 [1]. It represents 2% to 3% of chronic lymphoid leukemia cases, with a median age at diagnosis of 60 years and an equal male to female ratio [2]. Clinical symptoms typically consist of neutropenia and autoimmune manifestations and the lymphocytosis is often limited [3]. We report here the case of a patient who developed a rare bacterial infection in the setting of T-LGLL and discuss the possible pathogenetic implications of this previously unreported association.

CASE PRESENTATION

A 67-year old woman was followed in our unit since 11 years for T-LGLL revealed in 2002 by moderately increased lymphocytosis and neutropenia. The main history of this patient was an anxio-depressive syndrome leading to multiple hospitalizations in psychiatric unit. The initial assessment showed no superficial or deep lymphoid organ enlargement, but bone marrow and blood were infiltrated with CD3+/CD5+ lymphocytes expressing a non-specific translocation t(3;19)(p21;p13). Molecular study showed clonal rearrangement of the T cell receptor (TCR). Until December, 2012, lymphocytosis remained stable, as did neutropenia oscillating between 700 and 1500 neutrophils/mm^3. Several episodes of broncho-pulmonary infections were observed from 2007 to 2009, justifying punctual courses of filgrastim to maintain neutrophil count ≥1000 / mm^3, without modifying the attitude of abstention regarding the T-LGLL. This revealed beneficial and the infectious episodes have stopped.

In December, 2012, as her psychiatric disturbance worsened, the patient was put under anti depressive drugs (Miansérine chlorhydrate, Athymil ^{R}) which can cause agranulocytosis. Unsurprisingly, the neutropenia aggravated and stayed below 500 / mm3 over 3 weeks after Athymil ^{R} was stopped. Under Filgrastim, the neutrophil count improved, but, unsurprisingly, the response was transient, leading to two episodes of respiratory infection which were treated by amoxicillin then amoxicillin associated with clavulanic acid (AUGMENTIN^R), respectively. At discharge, a persistent hyperthermia associated with a dry

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cough was empirically treated by PYOSTACINE^{R} and SOLUPRED^{R}, then by ciprofloxacine (CIFLOX^{R}). One week later, she consulted in emergency unit for alteration of her general state, dyspnoea, persistent hyperthermia with cough and whitish sputum. On physical exam, bilateral pulmonary rales were found. There was no thoracic pain. A dyspnea was observed, but oxygen saturation was normal. There was no lymph node, liver or spleen enlargement. An empirical antibiotherapy with ROCEPHINE^{R}-OFLOCET^{R} was begun. CT-scan of the chest found centro-lobular nodules suggestive of bronchiolitis and infracentimetric nodes of the upper mediastinum with no pleural or pericardial effusion (Figures 1 and 2).

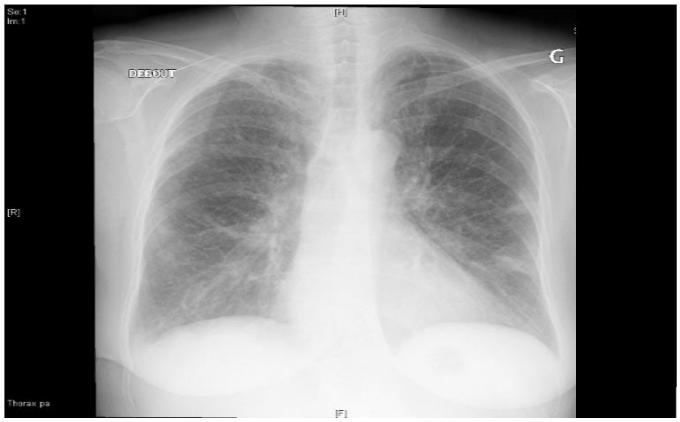

Figure 1: Initial chest X-ray showed bilateral interstitial infiltrates of the inferior lobes

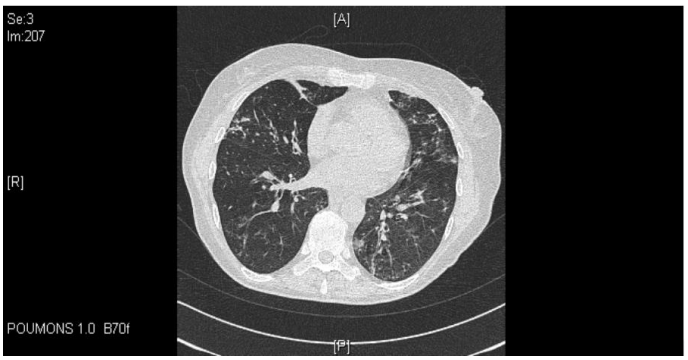

Figure 2: Initial CT-scan of the chest showed predominantly an aspect of bronchiolitis associated with an emerging aspect of focal lung condensation.

A bronchoalveolar lavage allowed the isolation of *Actinomyces odontolyticus*. After discussion with an infectiologist and a pneumologist, treatment schedule was defined as followed: amoxicillin (CLAMOXYL^{R}) intravenously at 12 gr / day for at least 4 weeks and, upon clinical and radiologic improvement, amoxicillin orally at 3 g / day as maintenance for at least six months. After 72 hours of antibiotic treatment with effective dose, we observed a regression of pulmonary rales and the disappearance of the cough. Response assessment by CT-scan by one month showed an important regression of the lung hurts.

Regarding the T-LGLL, treatment with cyclophosphamide (ENDOXAN^{R}) 100 mg / day during 4 months was succesfully implemented, resulting in a remarkable and sustained raise in neutrophil count above 1000 / mm3. No adverse effects and no additional infectious complications were observed.

DISCUSSION

The majority of patients with T-LGLL have a clinically indolent course. However, a significant fraction will develop neutropenia, anemia, recurrent bacterial infections, autoimmune disorders, or symptomatic splenomegaly [4]. Neutropenia, the most common hematologic disorder associated with T-LGLL, is the major reason for these patients seeking medical attention [5]. Approximately 70% to 80% patients with T-LGLL develop neutropenia and may be prone to infection. Anemia is the second most common hematologic disorder associated with T-LGLL. Another common association is autoimmunity, with rheumatoid arthritis occurring most often [6]. Although it has been suggested that LGLL cells represent cytotoxic T lymphocytes activated by chronic antigenic stimulation, the molecular mechanisms that lead to LGLL are unknown.

In several studies it was suggested that IL-15 might play a role in the pathogenesis of LGL leukemia. IL-15 is a pro-inflammatory cytokine, which is required for the genesis and homeostasis of natural killer cells or LGL [7]. IL-15 acts through a receptor composed of a β (CD122) and γ (CD132) chains, which it binds to with a high affinity to transmit its growth and activation signals in LGL [8].

The mechanism for neutropenia in patients with T-LGLL is unknown. However, increased expression of Fas ligand (FasL) in the serum, presumably hypersecreted by LGL, has been thought to play a central role [9]. The FasL gene is constitutively expressed in T-LGLL, and increased soluble FasL induces neutrophil apoptosis [10]. Interestingly, in some preclinical studies, the administration of high-dose IL-15 to rhesus macaques was also associated with a neutropenia [11]. IL-15 has been shown to induce polymorphonuclear neutrophil migration by triggering a cascade of cytokine and chemokine expression initiated through IL-18 [12]. In our patient, we did not assess such an hypothesis, but the neutropenia is probably linked to her leukemia and aggravated by neuroleptic medicine.

With regard to the pseudo-syndrome of Felty and its associated infectious risk, this patient does still not show, as in 2002, any lymphoid enlargement.

Actinomyces are a group of gram positive bacilli, predominantly anaerobic in nature. They frequently colonize the oral cavity and cause cervicofacial disease [13]. The most significant pathogen of this group is *A. israelii* which is usually associated with the cervico-facial and thoraco-pulmonary diseases [14]. However, *A. odontolyticus*, a less commonly recognized pathogen of the Actinomyces group, has been encountered in systemic infections such as peritonitis, brain abscess and thoracopulmonary infections [15]. *A. odontolyticus* is an anaerobic and capnoic gram positive bacillus that appears as thin filaments with or without branching. A very characteristic feature of this organism is the production of red colonies on blood agar. Like other members of Actinomyces, this organism also occurs as part of indigenous oral flora in humans. *A. odontolyticus* has been regularly isolated from dental caries and reported as an opportunistic pathogen associated with cervicofacial, abdominal and thoracic diseases as reported in the literature. Only few cases of thoracopulmonary infections due to *A. odontolyticus* were yet reported [16]. In this patient, there were no dental problems but the opportunistic character of the germ and the chronic neutropenia certainly favored this rare infection. There were respiratory clinical signs as productive cough, dyspnoea associated with

deterioration of the general status. Initial X-Ray and CT-scan of the chest clearly showed bilateral lung infection (Figures 1and 2). An intensive and long-term treatment with amoxicilline was necessary to clear the infection, as shown by control X-Ray (Figure 3).

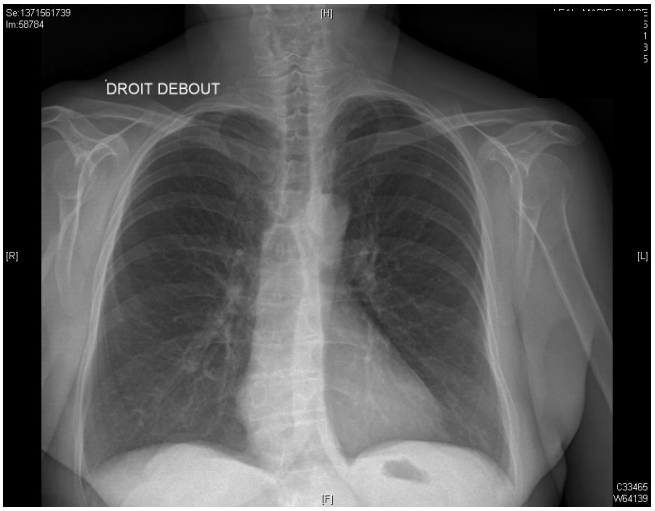

Figure 3: On chest control X-ray at 3 months of antibiotics, bilateral lung infiltrates had totally disappeared.

CONCLUSION

T-LGLL is a hematologic disease which can be responsible for severe neutropenia, opening the door to affections with rare and often opportunistic germs, which needs efficient and adequate treatment. Caution is recommended while prescribing drugs with neutropenic potential. Treatment with cyclophosphamide is a safe and efficient option.

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