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Granulomatous lung disease in a patient with a family history of hematological disorders

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Abstract. *Background:* A 29-year old patient presented with necrotizing granulomatous lung disease and a family history of myelodysplastic syndrome/acute myeloid leukemia. She appeared to be a carrier of a mutation in the transcription factor GATA2. The case adds to the recent described heterogeneous clinical manifestations and syndromes in which, against a background of hematologic disorders, GATA2 mutations have been demonstrated, such as the Monomac and Emberger syndromes. In patients with a granulomatous disease and a history of (familial) hematologic disorders, the occurence of GATA2 mutations should be considered, as to gain further insight in the occurrence of granulomatous disease in a possible distinct phenotype among GATA2 mutation carriers.
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Key words: Granulomatous disease, interstitial lung disease, GATA2 transcription factor, immunodeficiency, hematologic disease

A 29-year-old female was admitted to the pulmonary ward with progressive dyspnea, fever, intense thoracic pain at physical contact and interstitial lung anomalies. She had a history of recurrent pneumonias, furunculosis, mucocutaneous candidiasis and anogenital condylomata, positive for human papilloma virus. There were extensive verrucae vulgares on the digits of both hands. The blood count displayed a mild pancytopenia (Hb 11.2 g/dl; thrombocytes 76 $\times 10^9$/L; leukocytes 1.2×10^9/L; neutrophiles 0.64×10^9/L; lymphocytes 0.47×10^9/L; monocytes 0.02). A CT-scan of the thorax (Figure 1) showed interstitial pulmonary infiltrates, with a patchy, subpleural pattern of increased reticulation and traction bronchiectasis, especially in the apical areas. In the basal lung fields, some small, sharply defined non-perilymphatic nodules were observed. Moreover, there was a partly calcified mediastinal lymphadenopathy and bilateral pleural fluid. The pericardium was thickened. A PET-scan showed mild F-18-FDG uptake in mediastinal and abdominal lymph nodes, spleen and bone marrow. Neither immunologic bronchoalveolar lavage (BAL) nor endobronchial biopsy yielded specific data. Notably, there was no lymphocytosis, the CD4/CD8 ratio was normal, and no granulomas were observed in the endobronchial biopsies. Extensive culture and PCR-analysis of BAL fluid did not reveal active infectious disease. Serologic analysis on ANCA-associated disorders was negative.

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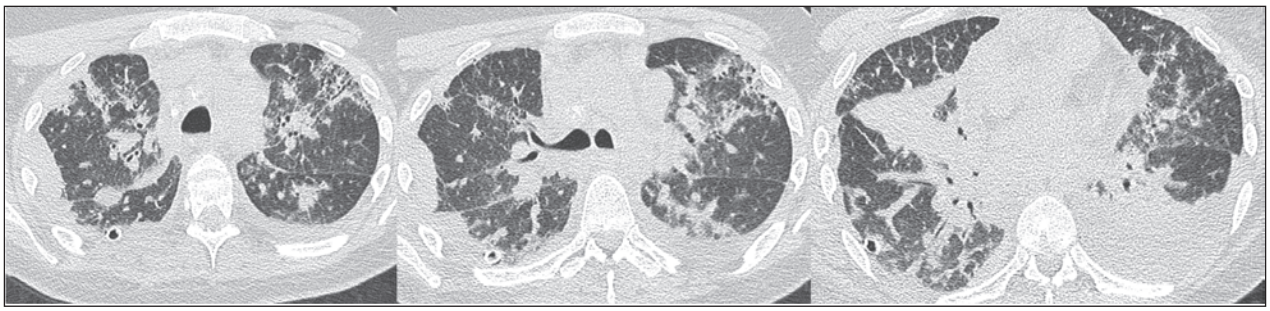

Fig. 1. Chest computed tomography scan of the lung demonstrating interstitial pulmonary infiltrates, with a patchy, subpleural pattern of increased reticulation and traction bronchiectasis, small, sharply defined nodules in the basal lung fields and asymmetric, bilateral pleural fluid.

Fever and dyspnea improved upon administration of antibiotics. However, the interstitial lesions did not change. Moreover, the bilateral pleural fluid accumulated. Repeated thoracocentesis revealed an alkalotic pleural fluid with a lymphocytosis. Repeated cultures of the pleural fluid remained negative, especially for (non-) tuberculous mycobacteria. Thoracotomy with biopsy of lung tissue (including nodules), pleura, pericardium and lymph node revealed a partly necrotizing granulomatous inflammation in all of the sampled tissue. Ziehl-Neelsen staining was negative. No vasculitis was observed. The patient started with glucocorticosteroids. The pleural fluid and the pericarditis diminished, however, neither the interstitial pulmonary infiltrates nor the pain did.

Further analysis of the hemogram demonstrated almost absent B- and NK-cells. T-cells were normal in number and function. IgG was slightly increased (1950 mg/dl), IgA and IgM levels were normal (180 mg/dl and 134 mg/dl, respectively). Angiotensin-converting enzyme level was normal (7 U/L). The bone marrow demonstrated dysplastic myelo- and erythropoiesis without excess of blasts or cytogenic abnormalities, fitting in with a myelodysplastic syndrome (MDS). In the bone marrow a few granulomas were observed; PCR analysis did not reveal either mycobacterium tuberculosis, or non-tuberculous mycobacteria (NTM).

After thorough history taking, the patient appeared to be part of a family with a large number of members with MDS or acute myeloid leukemia (AML) (the pedigree is recently described in (1). Therefore, she could be affected with a GATA2 mutation, a mutation recently associated with familiar MDS/AML (2). Indeed, subsequent analysis on the peripheral blood DNA of the patient and her father (diagnosed with MDS associated with monosomy 7 and an EBV-related peripheral T-cell non-Hodgkin lymphoma) revealed two GATA2 mutations (1).

During a follow-up period of more than three years, the clinical and radiologic picture remained stable under continuous glucocorticosteroid treatment. Recently, however, the patient presented with fever, weight loss and a new cervical lymphadenopathy, revealing, after cervical lymph node biopsy, a *Mycobacterium Kansasii*. The thoracic radiologic pattern remained unchanged.

Discussion

GATA2 is one of the so far identified genes playing a part in the development of familial MDS and/or AML (2). It is member of the family of GATA zinc finger transcription factors and predominantly expressed within hematopoietic stem cells (HSCs). Consequently, it is a pivotal player in the regulation of differentiation of HSCs into hematopoietic progenitor cells (3). Hence, mutations in the GATA2 transcription factor lead to myelodysplastic and/or leukemic disease.

Since the identification of GATA2 as a predisposition gene for familial MDS/AML, mutations have been found in other rare syndromes, displaying a spectrum of distinctive clinical features aside MDS/AML. The first is the syndrome of monocytopenia and mycobacterial disease (MonoMAC). The patients show decreased or absent monocytes, natural killer- and B-cells and is further characterized by disseminated nontuberculous mycobacterial

(NTM) disease, fungal disease and human papilloma virus infections (4). These patients develop MDS/MPD (chronic myelomonocytic leukemia) or AML. Pulmonary alveolar proteinosis appears to be a characteristic feature. Mutations in GATA2 have been reported in 20 MonoMAC patients (4). In these cases, NTM disease preceded the development of overt MDS by many years. This is in contrast with the presented case, where active *M. Kansassii* was detected years after developing MDS, and under long-term immunosuppressive therapy.

The absence of dendritic cells is designated as the dendritic cell-, mono-, and lymphopenia (DCML) syndrome and is also associated with GATA2 mutations (5). Ostergaard *et al*. described cases with features of the Emberger syndrome, which is associated with lymphedema consequent upon functional lymphatic hypoplasia, congenital deafness, hypotelorism and long tapering fingers. GATA2 mutations were associated with the development of MDS/AML and lymphedema in these patients (6). Recently, Ishida *et al*. reported a patient with clinical traits of both the MonoMAC and the Emberger syndrome (7), and a GATA2 mutation.

Since Hahn's publication in 2011 (2), succeeding reports concerning GATA2 mutation carriership draw a heterogeneous clinical picture. The recent report of the family members of the presented patient confirms that notion (1). Our patient expands the clinical picture with novel features. Although displaying similarities with the MonoMAC and Emberger syndromes and the case of Ishida *et al*., such as monocytopena, B-, and NK-cell lymphopenia, recurrent infections and warts at a background of GATA2 mutation in familiar MDS, other features like physical anomalies, edema, and at least in initially, the growth of NTM are absent. The most distinctive characteristic, however, is extensive, partly necrotizing, granulomatous inflammation in the pulmonary interstitium, lymph nodes, pleura, pericardium and bone marrow.

Granulomatous disease is described in infection, and the partly necrotizing component suspects infectious origin, as necrotizing granulomas are common in chronic infection, most notably in (non-) tuberculous mycobacteria and fungal disease. However, ample search by BAL cultures and in histopathologic tissue did not reveal active infection. Moreover, immunosuppressive therapy lead to clinical improvement. Signs of granulomatosis with polyangiitis, such as ANCA-positivity or histopathologic vasculitis, were not observed. There was no double breaking material in the sampled tissue. A diagnosis of necrotizing granulomatoid sarcoidosis was rejected because of the absence of vasculitis (8).

The origin of the granulomas in the present patient is hypothetical, as the underlying complex immunologic processes in non-infectious granuloma formation have as yet to be identified. Granulomas have been observed in other diseases with disturbed immune status, most extensively described in common variable immune deficiency (CVID), a syndrome marked by a decreased number of antibody-producing plasma cells (9). In CVID, a decreased proliferative response to antigens was found suggestive of a disturbed T-cell function, suggesting that antigen processing defects and imbalance of cytokine production lead to abnormal sequestration of antigen and subsequent granuloma formation. Possibly similar mechanisms of defective antigen processing occurred in the present patient, with a role for a high antigen load due to recurrent infection. Indeed, in sarcoidosis, there is an important role for infectious agents such as propionibacterium acnes and mycobacteria in granuloma formation. This process is regulated by a complex interaction induced by polarized CD4+ cells with a Th-1 immunophenotype and macrophages, with an important role for cytokines like tumor necrosis factor-α (10). In this report, similarities with CVID include radiologic features such as non-perilympatic nodules and bronchiectasis (11), while lacking more sarcoidosis-specific features such as perilymphatic nodules, lymphocytosis and increased CD4/CD8 ratio in immunologic BAL. Whether the extensity of the granulomatosis should be viewed as a systemic sarcoidosis is therefore debatable and as such the granulomatosis in the presented report may be considered as a sarcoid-like reaction. The association with granulomatous lung disease and thoracic pain has been recognized (12).

Despite the recentness of appreciation and the rareness of appearance of GATA2 mutations in familial MDS/AML and related disease entities, at present it is clear that there is a wide spectrum of clinical manifestations in GATA2 mutation carriership. This first description of extensive granulomatosis in a patient with familial MDS/AML and a germline mutation in GATA2, adds to this notion,

and implicates the recommendation to consider GATA2 analysis in patients with granulomatous disease at a background of familiar MDS/AML and monocytopenia and lymphopenia, as to further scout the occurrence of granulomatous disease as a (part of a) distinct phenotype among GATA2 mutation carriers.

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