Background: The TET2 gene encodes ten-eleven translocation methylcytosine dioxygenase 2 (TET2). TET2 is an epigenetic regulator that converts 5-methylcytosine to 5-hydroxymethylcytosine and also intersects with histone-modifying enzymes and transcription factors. Somatic mutations in TET2 are early events in clonal expansion and are found in association with myeloid and lymphoid hematological diseases. Germline mutations in TET2 have only been described in 3 children of consanguineous parents. These mutations led to immunodeficiency and lymphoma and early mortality in childhood.

Objectives: To assess the clinical and immunological consequences of a combination of a germline and a somatic mutation in TET2.

Methods: Genetic analysis was done by whole exome sequencing. An in-depth immunological analysis was performed.

Results: Clinical phenotype: The patient of non-consanguineous parents presented at the age of 38 with axial spondyloarthritis. Apart from trace homogeneity, his condition improved after the TNF-inhibitor was changed to an IL-17-inhibitor combined with prednisone (up to 40 mg). His lymphadenopathy persisted and the patient recurrently suffered from fevers, fatigue and pleurisy. Lymphnode biopsies showed no signs of malignancy. The patient had recurrent episodes of pancytopenia that spontaneously improved and he developed two episodes of pneumonia. Furthermore, he suffered from recurrent episodes of herpes zoster.

Immunological results: On immunologic work-up the patient had a polyclonal hypergammaglobulinemia and autoantibody testing revealed a homogenous ANA (1:1600), and positive anti-nucleosomen-, anti-PM-Scl70-, anti-SS-A, anti-PL-12-, anti-phospholipid-, anti-dsDNA- and anti-MPO-autoantibodies. Despite of increased amounts of immunoglobulins the patient developed a progressive and persistent loss of B cells (Figure 1), with an increased expression of CD80/86 on the remaining memory B cells. Within the T cell compartment double-negative T cells were increased.

Results of whole exome sequencing: Whole exome sequencing revealed a germline mutation in TET2 with the variant c.3641G>A; p.Arg1214Gln in the heterozygous state (NAF 0.53; NM_001172078.3). This mutation affects a phylogenetically conserved amino acid and is classified as predominantly pathogenic in the in silico prediction. Another variant identified is the mutation c.1864C>T; p.Gln622X, which leads to the emergence of a stop codon (NAF 0.41). This variant was only detectable as a low-grade mosaic (5-10%) in the buccal mucosa in the control, possibly as a result of lymphocytic infiltration into the buccal mucosa. In leukocytes, this mutation was detectable in 83% of cells in the heterozygous state. Both mutations have a low frequency in the population (1-2/1230000-1500000; gnomAD).

Hematological malignancy: 5 years after the progressive loss of B cells had started, the patient was diagnosed with a follicular B cell lymphoma and shortly after with AML with myelodysplasia-associated changes (AML-MRC). A familial-allogenic peripheral blood stem cell transplantation was performed. During the next 6 months follow-up no relapse occurred.

Conclusion: Combined heterozygous germline and somatic mutations in TET2 are associated with a very complex phenotype combining autoimmunity, lymphoproliferation and hematological malignancy, may present in adulthood and thus clinically differ from combined heterozygous germline mutations with early onset in childhood.

REFERENCES:

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PO05984 DARATUMUMAB RESCUE THERAPY IN A PATIENT WITH ANTI-MDA5 ASSOCIATED ARDS

Keywords: Myositis, Lungs, Autoantibodies

L. Ostendorf1,2, F. Münch1, L. Thormählen3, J. Nee1, U. Schneider4.

1Charité – Universitätsmedizin Berlin, Department of Nephrology and Medical Intensive Care, Berlin, Germany;
2Deutsches Rheuma-Forschungszentrum Berlin (DRFZ), ein Institut der Leibniz-Gemeinschaft, Autoimmunity, Berlin, Germany;
3Charité – Universitätsmedizin Berlin, Department of Cardiology, Angiology and Intensive Care Medicine, Berlin, Germany;
4Charité – Universitätsmedizin Berlin, Department of Rheumatology and Clinical Immunology, Berlin, Germany

Background: MDA5-associated dermatomyositis is often associated with rapid progressive interstitial lung disease resulting in acute respiratory distress syndrome (ARDS). Patients that progress to require mechanical ventilation or extracorporeal membrane oxygenation (ECMO) generally have a high mortality despite intensive combined immunosuppressive treatment. (1) Daratumumab, an anti-CD38 monoclonal antibody has been successfully used in the treatment of refractory autoantibody-associated diseases with the intention of targeting autoantibody-producing CD38+ plasma cells. (2)

Objectives: Rescue treatment of anti-MDA5 antibody associated ARDS with Daratumumab combination therapy.

Methods: We treated an ECMO-dependent patient with refractory anti-MDA5 dermo-pulmonary syndrome with a combination treatment of four weekly doses of 1800mg daratumumab s.c. as well as tofacitinit, ciclosporin and prednisolone.

Results: A 55-year-old patient was transferred to our hospital with ARDS of unknown origin combined with a short history of oligoarthritis and Gottron's papules. She required mechanical ventilation and ECMO. Autoantibodies showed strong positivity for anti-MDA5 and -Ro/S2, so she was diagnosed with MDA5 dermatopulmonary syndrome. She initially received treatment with cyclophosphamide, tofacitinit, ciclosporin, intravenous immunoglobulins and high-dose steroids. However, her intestinal lung disease showed no improvement. We escalated the immunosuppressive therapy with daratumumab. The pulmonary function improved approximately four weeks after daratumumab initiation and the patient was consequently weaned from ECMO and respirator. The clinical course was complicated by an ischemic stroke and a blood stream infection with enterococci which would have made a lung transplantation impossible. We were able to discharge the patient to rehabilitative care with only low-flow supplemental oxygen.

Conclusion: Rescue immunosuppressive therapy of MDA5-antibody associated ARDS with daratumumab in addition to tofacitinit, ciclosporin and prednisolone was associated with remarkable clinical improvement in this case. More clinical data and long-term follow-up are needed to investigate safety and efficacy of this treatment regimen in MDA5-antibody-associated disease.

REFERENCES:

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Psychosocial support

PO0985-PARE FACTORS ASSOCIATED WITH FEELINGS OF GUILT AND SHAME IN PATIENTS WITH PSORIATIC ARTHRITIS

Keywords: Mental health, Skin, Psoriatic arthritis

Figure 1.