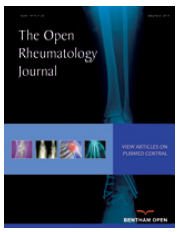

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Supplementary Material

Rituximab for the Treatment of Common Variable Immunodeficiency (CVID) with Pulmonary and Central Nervous System Involvement

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1. GENETIC DIAGNOSTICS

There are several mutations described which can cause a CVID-like syndrome and can predispose to GLILD like LRBA, CTLA4, RAG1, BIRC4, NFKB1 or KMT2D [1 - 9]. Genetic testing was performed on one patient revealing a gain of function mutation of STAT3. GOF-STAT3-syndrome is a relatively new described syndrome and can cause a CVID-like disease with hypogammaglobulinemia, autoimmune features, lymphoproliferation, and interstitial lung disease [10].

2. HISTOPATHOLOGIC FINDINGS

Patient 1: In 2010, a lung biopsy was performed in an external clinic revealing dense lymphoid infiltrates in histologic testing. A follicular arrangement of CD20-positive B cells and CD3-positive T cells was described without S100 or CD30 positive cells. Re-biopsy in 2013, presented a heterogeneous pattern consisting of NSIP and chronic and partly follicular bronchiolitis. No evidence of malignancy.

Patient 2: In 2009, we performed a biopsy on the right lower lobe of the lung. Histologic examination presented medium-sized epithelioid cell granuloma. In the granuloma wall, loosely scattered CD20 positive B lymphocytes mixed with CD5 positive T cells were found. Poorly present plasma cells without light chain restriction. No evidence of malignancy.

Patient 3: VATS with wedge resection for histologic sampling was performed in 2017. Wedge resection on the upper lobe showed the histologic image of a lymphoplasmohistiocytic infiltration. Wedge resection of the left lower lobe also presented the same chronic lymphoplasmohistiocytic infiltration. Histologic presentation of a mixed image of dominating CD5-positive T cells with CD20-positive B cells in the background with partly loose and follicular aggregation. Low level of plasma cells without light chain restriction. No evidence of malignancy.

3. B CELL REGENERATION CORRELATED WITH GLILD RELAPSE AFTER RITUXIMAB-TREATMENT

Table 1. Flow cytometric analysis of peripheral blood during rituximab-therapy.

Flow cytometric analysis	
Patient 1:	
4x rituximab 375mg/m^2 09/2007	
Flow cytometry pre-rituximab 06/2006: 14% B cells, 27% naïve CD10$^+$ B cells, low count of memory B cells, 1.3% postswitch memory B cells, normal count of CD21low B cells.	Flow cytometry post-rituximab 10/2007: No B cells detectable
2x rituximab 1g abs. 08/2010	
Flow cytometry pre-rituximab 06/2010: 5% B cells. No memory B cells, normal count of transitional B cells.	Flow cytometry post-rituximab 09/2010: No B cells detectable
2x rituximab 1g abs. 08/2014	
Flow cytometry pre-rituximab 03/2014: 4.7% B cells. No increase of transitional B cells, complete loss of memory B cells.	Flow cytometry post-rituximab 09/2014: No B cells detectable
2x rituximab 1g abs. 09/2015	

Flow cytometric analysis	
Flow cytometry pre-rituximab 01/2015: 1% B cells. No further sub differentiation possible.	Flow cytometry post-rituximab 05/2016: No B cells detectable
2x rituximab 1g abs. 06/2017	
Flow cytometry pre-rituximab 08/2016: Very low count of B cells	Flow cytometry post-rituximab: Not performed
2x rituximab 1g abs. 01/2019	
Flow cytometry pre-rituximab 10/2018: Very low count of B cells (<0.1%)	Flow cytometry post-rituximab Not performed
2x rituximab 1g abs. 10/2019	
Flow cytometry pre-rituximab Not performed	Flow cytometry post-rituximab 12/2019: No B cells detectable
Patient 2:	
2x rituximab 1g abs. 09/2014	
Flow cytometry pre-rituximab 02/2014: 7% B cells, 5.2% transitional B cells, 8.6% preswitch memory B cells. 1% postswitch memory B cells. No CD21-positive population.	Flow cytometry post-rituximab 11/2014: No B cells detectable
2x rituximab 1g abs. 02/2017	
Flow cytometry pre-rituximab 08/2016: 3% B cells	Flow cytometry post-rituximab 08/2017: No B cells detectable
Patient 3:	
2x rituximab 1g abs. 07/2017	
Flow cytometry pre-rituximab 06/2017: 2.7% B cells. No preswitch and postswitch memory B cells. Increase of transitional B cells, no increase of CD21low cells.	Flow cytometry post-rituximab 11/2017: 1.5% B cells
2x rituximab 1g abs. 01/2018	
Flow cytometry pre-rituximab 11/2017: 1.5% B cells	Flow cytometry post-rituximab 03/2018: Low count of B cells (0.2%), no sub differentiation possible
2x rituximab 1g abs. 09/2018	
Flow cytometry pre-rituximab 08/2018: 8.5% B cells.	Flow cytometry post-rituximab 12/2018: 1,7% B cells. Almost complete as transitional B cells. 6.2% preswitch and no postswitch memory B cells.

Table S2. List of GLILD-patients.

Patient	Gender	EUROclass subtype	autoimmune Cytopenia	Treatment
1	male	B+SmB-CD21^{norm}T^{norm}	No	IgRT
2	male	B+SmB-CD21^{norm}Tr^{high}	Yes	Prednisolone, azathioprine
3	female	B+SmB-CD21^{norm}Tr^{norm}	Yes	Prednisolone only
4	female	B+SmB-CD21^{norm}Tr^{norm}	Yes	Prednisolone, azathioprine, rituximab
5	female	B+SmB-CD21^{norm}Tr^{norm}	Yes	Prednisolone, azathioprine, rituximab
6	female	B+SmB-CD21^{norm}Tr^{norm}	Yes	Prednisolone, rituximab, combination of rituximab and azathioprine, rituximab.

Table S3. Contingency table for cytopenia and GLILD

-	CVID-patients with autoimmune cytopenia	CVID-patients without autoimmune cytopenia
CVID-patients with GLILD	**5**	**1**
CVID-patients without GLILD	**11**	**33**

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