The therapeutic response in Gorham’s syndrome to the beta-blocking agent propranolol is correlated to VEGF-A, but not to VEGF-C or FLT1 expression

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Abstract

Background: Gorham’s syndrome is a rare illness of unknown etiology. It is characterized by a local proliferation of blood or lymphatic vessels that leads to progressive resorption and destruction. The cause of the disease is not elucidated, and therapeutic options remain limited.

Case presentation: We report herein the case of a young female Caucasian patient aged 18 years with diffuse Gorham syndrome. In tissue specimens angiogenesis and massive lymphangiogenesis as well as the expression of vascular endothelial growth factor-A (VEGF-A) and neuropilins was observed. Lymphangiogenesis is a prominent feature of the disease and a number of lymphatic markers were found to be expressed, however only VEGF-A, but not vascular endothelial growth factor-C (VEGF-C) was found to be elevated in the circulation. Circulating levels of soluble VEGF receptor-1 were also not elevated. Furthermore, the patient responded favorably and the disease was stabilized following treatment with the beta-blocking agent Propranolol alone which acts on VEGF-A alone, but not on soluble VEGF receptor-1 levels.

Conclusion: This suggests that the disease is dependent on VEGF-A, but on neither VEGF-C, the major driver of lymphangiogenesis, nor FLT1. Furthermore, Propranolol acts on VEGF-A but not FLT1 expression.

Keywords: Gorham’s syndrome, VEGF, Angiogenesis, Lymphangiogenesis
to be elevated in the patient’s circulation. Circulating levels of soluble FLT-1 were also not elevated. Furthermore, the patient responded favorably to the β-blocking agent Propranolol which acts on VEGF-A, but not on FLT-1 levels. Clinical symptoms were already present at the age of 9. At diagnosis at the age of 15, the patient exhibited pronounced diffuse lesions in bone and soft tissue (Figure 1a). Furthermore, this was accompanied by severe gynecological symptoms with loss of chylous/lymphatic liquid. Biopsies of cervical lesions revealed pronounced angiogenesis and lymphangiogenesis (Figure 1b). VEGF-A was strongly expressed at the site of the lesion along with neuropilin 1

**Figure 1** a Radiological images of spleen (upper image) and pelvic region (lower image) at diagnosis. Multiple hypodense nodules are present in the spleen and fluid accumulation in the pelvic region is seen. b Immunohistochemistry of cervix tissue for blood and lymphatic vessel markers. Blood vessels were revealed by cluster of differentiation 31 and 34 (CD31, CD34), neuropilin-1 (NRP1, arterial marker), neuropilin-2 (NRP2, venous marker) immunostaining. Lymphatics were detected by Lymphatic vessel endothelial hyaluronan receptor-1 (LYVE-1) and Podoplanin immunostaining. Blood and lymphatic vessels are detected both by CD31 and NRP2 immunostaining. Furthermore, VEGF-A was significantly expressed in the tissue. Areas in the dotted squares are shown at higher magnification in the right hand images for each marker. Scale bars: Left panels 50 µm, right panels 20 µm. c Detection of vascular endothelial growth factor-A (VEGF-A) and soluble fms-like tyrosine kinase (FLT-1) in plasma samples by ELISA. VEGF-A (black dots) and FLT-1 (blue triangle). We noticed a decrease in VEGF-A levels between July 2013 and May 2014 (after Propranolol treatment) compared to April 2013 (before treatment). No significant change was observed for FLT-1. Vascular endothelial growth factor-C (VEGF-C) was below detection limit in all samples. Control levels of healthy donors were 75.78 pg/ml and 20.58 ng/ml for VEGF-A and FLT-1 respectively (pooled sample, n = 6).
may be due to transient treatment interruption by the 12 months of treatment. The rebound effect at 7 months was observed which subsequently decreased again after 7 months of treatment, some increase in VEGF-A levels after 3 months of treatment to nearly control levels. At stabilization of bone lesions. VEGF-A levels dropped with a disappearance of gynecological symptoms and initiated. The patient responded well to this treatment higher in patients with lymphatic malformation in comparison to control samples. Lymphatic malformation and Gorham's syndrome are not the same clinical entities which may explain the differences observed.

Treatment with Propranolol LP (2 mg/kg/day) was initiated. The patient responded well to this treatment with a disappearance of gynecological symptoms and stabilization of bone lesions. VEGF-A levels dropped after 3 months of treatment to nearly control levels. At 7 months of treatment, some increase in VEGF-A levels was observed which subsequently decreased again after 12 months of treatment. The rebound effect at 7 months may be due to transient treatment interruption by the patient since the heart rate increased during that period.

Morimoto et al. [5] have demonstrated that a combination treatment including surgery, interferon and Propranolol is able to improve the clinical evolution of Gorham's syndrome. Furthermore, they showed with a single measurement (time point) that the combination of surgery, interferon and Propranolol™ is able to decrease VEGF-A levels. In opposition to these results, we demonstrate that Propranolol alone is able to improve clinical outcome and decreases VEGF-A levels measured at several time points. Soluble FLT1 could also explain the therapeutic effect because soluble FLT1 is an endogenous inhibitor of VEGF-A. However, soluble FLT1 is not up-regulated after Propranolol treatment. Nir et al. [4] described an effect of Propranolol on clinical outcome, but the study did not include measurement of VEGF family members or other angiogenic factors.

Conclusions
Our results suggest that, despite pronounced lymphangiogenesis, Gorham's syndrome seems to be dependent on VEGF-A and not on VEGF-C or FLT-1. Furthermore, this case demonstrates that Propranolol can be safely administered and has striking therapeutic efficacy as a single agent in Gorham's syndrome by decreasing circulating VEGF-A but not by modifying VEGF-C or FLT-1 levels.

Additional file

Additional file 1: CARE Checklist (2013) of information to include when writing a case report.

Abbreviations
CD31: cluster of differentiation 31; CD34: cluster of differentiation 34; LYVE-1: lymphatic vessel endothelial hyaluronan receptor-1; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor; FLT1: fms-like tyrosine kinase-1; NRP: neuropilin.

Authors’ contributions
JB and AL performed experiment. DG provided patient materials (clinical data, tissue samples). AB designed the study and wrote the article. JB, AB, AL and DG analyzed the data. All authors read and approved the final manuscript.

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Compliance with ethical guidelines
The authors declare that they have no competing interests.

Consent
“Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.”

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(NRP1) and 2 (NRP2) (Figure 1b). Plasma VEGF-A levels were found to be increased by threefold in comparison to a pool (n = 6) of young healthy female donors (control 75.13, versus 233.42 pg/ml for the patient). VEGF-A levels before treatment were higher than those reported in breast cancer patients (136.22 ± 9.95 pg/ml) [7]. The CARE Checklist (2013) of information is included in Additional file 1.
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