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Brief Report

Low periostin levels in adult patients with Langerhans cell histiocytosis are independently associated with the disease activity

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ABSTRACT

Purpose. Langerhans cell histiocytosis (LCH) is a rare proliferative disease of cells of the CD1a+/CD207+ myeloid dendritic cell lineage that may infiltrate one or more organs or systems at all ages. We aimed to evaluate periostin and sclerostin serum levels in adult patients with LCH.

Procedures. This was a cross-sectional study comparing 38 adult patients with LCH with 38 age- and sex-matched healthy controls. Serum periostin and sclerostin levels were measured to compare between LCH patients and controls as well as between patients with active and non-active disease.

Results. Serum periostin levels were significantly lower in LCH patients than controls (457 ± 72 ng/ml vs. 721 ± 79 ng/ml, $p = 0.014$) but this was not the case for sclerostin levels which did not differ between patients and controls, respectively (29.0 ± 1.8 pmol/L vs. 39.5 ± 3.8 pmol/L, $p = 0.12$). Patients with active disease had significantly lower periostin levels than those with inactive disease (240 ± 78 ng/ml vs. 558 ± 94 ng/ml, $p = 0.008$). No effect of specific site involvement, extend of disease, or treatment administered was found on any of the above parameters measured.

Conclusions. Lower serum periostin levels were observed in adult LCH patients with active disease. The finding warrants further investigation to define whether periostin could serve as a serum biomarker for LCH activity.

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Abbreviations: BMI, body mass index; CTX, C-terminal telopeptide of type I collagen; IL, interleukin; LCH, Langerhans cell histiocytosis; PINP, procollagen type I N-terminal propeptide; PTH, parathyroid hormone.

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1. Introduction

Langerhans cell histiocytosis (LCH) is a rare proliferative disease of cells of the CD1a+/CD207+ myeloid dendritic cell lineage that may infiltrate one or more organs or systems at any age [1,2]. Although predominantly described in children, recently adults with LCH are increasingly been identified [1,3]. Management of LCH in adults ranges from local therapy in patients with single site disease to systemic chemotherapy in cases of multisystem disease [4]. There is evolving evidence that antiresorptive bone agents are active in patients with skeletal involvement [4–6].

Periostin, a secreted extracellular matrix protein, is expressed in collagen rich connective tissues and interacts with several cell surface integrin molecules, providing signals for tissue development and remodeling [7]. In the skeleton, periostin stimulates osteoblast activity and bone formation in mice, through inhibition of sclerostin production and subsequent stimulation of the canonical Wingless (Wnt)/β-catenin pathway [8]. On the contrary, in humans periostin is associated with increased fracture risk [7], albeit without correlation with bone mineral density [9,10] suggesting an effect on the organic rather than mineral component of the skeleton. Besides its effects on bone, periostin has been considered as a potential biomarker of metastatic disease, several inflammatory processes and organ dysfunctions [11].

Sclerostin, is a negative regulator of the Wnt/β-catenin signaling, inhibiting osteoblastic bone formation. Sclerostin is considered to be almost exclusively produced by the osteocytes [12], but can also be found in other tissues mainly the kidneys, liver, heart and lungs [13].

As skeletal involvement is common in adults with LCH [4] and bone metabolism is also affected during the course of the disease [14], alterations of periostin and sclerostin may be involved in the pathogenesis of the disease or be affected by the disease's processes. The aim of the present study was to evaluate serum levels of periostin and sclerostin in adults with LCH, in an attempt to delineate if they have a role in the pathogenesis of the disease and identify potential implications.

2. Patients and Methods

2.1. Patients and Methods

In this cross-sectional study, 38 patients with LCH and 38 healthy age, sex, and BMI matched individuals were included, excluding potential confounding parameters, such as metabolic bone disorders, underlying malignancy and renal impairment, as previously described [14]. Disease's state was defined as "active" in the presence of disease-related signs/symptoms with or without appearance of new lesions. Both patients and controls were not receiving any medication known to affect bone metabolism.

Early morning fasting blood samples were collected from all subjects. Circulating periostin (USCN, Houston, TX), sclerostin (Biomedica, Vienna, Austria), procollagen type I N-terminal propeptide (PINP; USCN, Houston, TX), and C-terminal telopeptide of type I collagen (CTX; IDS, Boldon, UK) levels were measured with enzyme-linked immunosorbent assay (ELISA) on samples stored at −80 °C. Parathyroid hormone (PTH) was measured in patients with 25-hydroxyvitamin D values <50 nmol/L for the exclusion of secondary hyperparathyroidism. Basal hematological and biochemical analysis, C-reactive protein, and erythrocyte sedimentation rate (ESR) estimation were performed by semi-automated assays. The study was approved by the local institutional committee and is in accordance with the guidelines of the Declaration of Helsinki; written informed consent was obtained from all subjects.

2.2. Statistical Analysis

Continuous data are presented as mean ± standard error of the mean (SEM). Categorical data are presented as absolute numbers and/or frequencies. Kolmogorov–Smirnov test was used to check the normality of distributions of continuous variables. Independent samples T-test or Mann–Whitney test was used for between group comparisons. Analysis of variance (ANOVA) was used for between group comparisons. Bonferroni post-hoc correction was used for multiple pairwise comparisons. Chi-square or Fisher's exact test was used to compare categorical variables. Spearman's coefficient (r's) was used for bivariate correlations. For regression analysis, variables with skewed distribution were logarithmically transformed. In all the above mentioned tests, $p < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS 21.0 for Macintosh (IBM, Armonk, NY).

3. Results

3.1. Comparisons Between Groups

Serum periostin levels were significantly lower in LCH patients than controls whereas there was no difference in sclerostin, P1NP and CTX levels (Table 1).

When patients were divided into those with active and inactive disease, a significant decrease in periostin levels was associated with disease activity (Table 2; $p = 0.008$). In pairwise comparisons, LCH patients with active disease had significant lower periostin levels compared to controls ($p = 0.007$), but not compared to patients with inactive disease ($p = 0.50$) (Supplemental Fig. 1A). Sclerostin levels as well as P1NP and CTX were similar between patients with active and inactive disease (Table 2 and Supplemental Fig. 1B).

No significant difference in periostin, sclerostin, P1NP or CTX levels was observed between patients with or without bone involvement or other organ involvement (Table 2). Serum periostin and sclerostin levels were not different between treatment naïve and treated LCH patients irrespective of the treatment utilized.

3.2. Correlations of Periostin and Sclerostin Levels

Periostin and sclerostin levels were inversely correlated in the control group (r's = −0.52; $p = 0.001$), but not the LCH group

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