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SHORT COMMUNICATION

Chitinase-3-like Protein 1 (YKL-40): Novel Biomarker of Hidradenitis Suppurativa Disease Activity?

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Hidradenitis suppurativa (HS) is a recurrent, debilitating, suppurative skin disease of intertriginous regions with an estimated prevalence of 1% and female predominance (1). According to Jemec (2), HS quantification is still clinical. There are some scoring systems for assessment of disease severity (e.g. Hurley staging, Physician's Global Assessment, Sartorius score) and treatment effectiveness (HiSCR); however, all of them have some limitations in daily practice (2, 3). Biomarkers that could facilitate differentiation between disease stages and, more importantly, evaluation of disease progression/regression, are still not available for routine use. Recently, soluble IL-2 receptor (sIL-2R) and myeloid marker S100A8/A9 were suggested as acceptable biomarkers in HS (4, 5). Here we suggest a new biomarker, chitinase-3-like protein 1 (YKL-40), which has never been studied in HS before. YKL-40 is secreted by chondrocytes and synovial cells. It is also expressed by mature neutrophils, endothelial cells and macrophages. However, the exact biological function of YKL-40 is not fully known – it is suggested to participate in angiogenesis, mitogenesis, proliferation and remodelling. Therefore, YKL-40 has been involved in studies of cancers, cardiovascular diseases (CVD), infections and other inflammatory disorders, such as arthritis, inflammatory bowel disease or even some dermatoses (e.g. psoriasis) (6, 7).

MATERIAL AND METHODS

Our study was conducted on a group of 61 consecutive patients (30 women, 31 men) 17–72 years of age (mean 38.4 ± 11.4 years) suffering from HS diagnosed in accordance with the well established clinical criteria (8). The disease duration ranged from 2 to 27 years (mean 8.6 ± 7.3 years). Clinical manifestation of disease staging was based on the three-degree scale proposed by Hurley (9) (Table I). The mean body mass index (BMI) of 28.8 ± 5.0 kg/m^2 qualified our patients as overweight. The active/ex-smoker rate amounted to 62.3%. All patients with any significant comorbidities or receiving any systemic treatment (>5 half-lives washout period), which could interfere with the studied parameters, were excluded. Twenty-six healthy volunteers aged 40.2 ± 10.5 years (range 28–60 years) constituted the control group (BMI = 25.8 ± 5.9). The control subjects matched for age, race and gender were randomly selected from the individuals of a survey population who did not declare that they had HS or any other significant diseases or therapies.

The ELISA kits were used to quantify YKL-40 (R&D Systems, Minneapolis, USA; DC3L10) and sIL-2R (eBioscience, San Diego, USA; BMS212/2CE) serum concentrations (For further details see Appendix S1[1]).

RESULTS

The mean YKL-40 serum level was 50.5 ± 49.6 ng/ml and 26.4 ± 20.3 ng/ml for patients and controls, respectively ($p < 0.001$). ROC analysis showed an area under the curve (AUC) of 0.73. The optimal cut-off value for YKL-40 was 17.8 ng/ml with positive (PPV) and negative predictive values (NPV) of 0.80, 0.71, respectively. Statistically significant differences ($p < 0.001$) in YKL-40 serum concentrations between Hurley groups were also found. The patients with more severe disease had a markedly elevated serum level of YKL-40 (Table I). The multivariate analysis of variance revealed that neither gender, age, BMI nor smoking were determining factors for YKL-40 serum concentration. Additionally, we found that in HS patients YKL-40 was correlated with CRP ($R = 0.55$, $p < 0.0001$) and white blood cells (WBC) ($R = 0.37$, $p = 0.008$). The results for sIL-2R were quite concordant with these obtained for YKL-40 ($R = 0.46$, $p = 0.0002$). The mean sIL-2R serum level of the HS patients was 5.2 ± 2.9 ng/ml, whereas in healthy volunteers it was significantly lower (3.3 ± 1.4 ng/ml, $p = 0.001$). ROC analysis revealed an AUC of 0.72. The optimal cut-off point was estimated as 2.8 ng/ml with PPV and NPV of 0.80, 0.59, respectively. Our earlier research demonstrated that the level of serum sIL-2R increased significantly with disease stage (4). In the present study, in contrast to the previous one, we did not find any significant differences in sIL-2R levels between different Hurley groups ($p = 0.1$). However, there was still an increasing trend of sIL-2R serum levels related to more severe disease (Table I).

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Table I. *Serum levels of chitinase-3-like protein 1 (YKL-40), soluble interleukin 2 receptor (sIL-2R), white blood cells count (WBC) and C-reactive protein (CRP) in healthy controls and patients with hidradenitis suppurativa according to Hurley grading system*

	n (F/M), smoking rate	YKL-40 (ng/ml)[a] Mean ± SD (range)	sIL-2R (ng/ml) Mean ± SD (range)	WBC (×10^3/mm^3)[b] Mean ± SD (range)	CRP (mg/l)[a] Mean ± SD (range)
Controls	26 (16/10), 12%	26.4 ± 20.3 (7.4–104.8)	3.3 ± 1.4 (1.5–6.4)	7.0 ± 1.5 (3.9–9.7)	2.8 ± 1.9 (0.2–7.8)
Hurley I	20 (11/9), 45%	26.6 ± 10.5 (11.8–53.8)	4.6 ± 2.1 (1.9–10.1)	6.8 ± 1.6 (4.3–9.3)	2.8 ± 3.0 (0.2–10.7)
Hurley II	29 (17/12), 66%	48.7 ± 48.1 (8.5–212.5)	4.9 ± 2.7 (1.5–14.6)	9.0 ± 2.8 (3.4–14.6)	9.9 ± 10.4 (0.8–39.6)
Hurley III	12 (2/10), 92%	94.5 ± 64.8 (20.5–214.0)	7.1 ± 3.9 (1.9–14.4)	10.8 ± 3.2 (8.0–18.5)	49.8 ± 36.7 (7.0–116.1)

[a]Statistically significant difference between Hurley I and III, and between Hurley II and III. [b]Statistically significant difference between Hurley I and III.

The mean WBC in HS group was $8.8 \pm 2.9 \times 10^3$ mm^{-3}. Seventeen (27.9%) patients had leucocytosis. According to ROC, cut-off point was established as 7.06×10^3 mm^{-3}. AUC, PPV and NPV were as follows: 0.69, 0.76 and 0.58, respectively. CRP mean value was 16.4 ± 25.5 mg/l (one outlier excluded) and was elevated above the normal range in 34 (55.7%) patients. ROC analysis revealed CRP of 0.3 mg/l as the cut-off value with AUC, PPV and NPV of 0.69, 0.65 and 0.67, respectively.

DISCUSSION

In this study WBC and CPR serum levels were within the normal range in 72% and 45% of patients, respectively. Moreover, the AUC, PPV and NPV were lower than for YKL-40 or sIL-2R.

YKL-40 seems to be more useful for monitoring the grade of inflammation in HS than the other laboratory markers, including CRP, which is the most relevant marker currently used for this purpose in routine practice. Noteworthy, the patients with higher Hurley stage had significantly increased serum level of YKL-40. The elevation of YKL-40 levels might have resulted from bacterial superinfection and skin changes with the involvement of potent proinflammatory cytokines that induces migration of phagocytic cells (10, 11) or some non-specific factors, secondary to the somewhat general inflammatory response being an exponent of systemic changes. Although none of the patients fulfilled criteria for metabolic syndrome, HS sufferers are more prone to its development due to the common genetic/environmental factors or shared inflammatory pathways (12, 13). Similarly to an increased level of CRP, which has been shown to be a predictor of the CVD and metabolic syndrome risk, the YKL-40 has also been suggested as a possible biomarker of inflammation and endothelial dysfunction in CVD (14). Increased circulating and visceral adipose tissue expression levels of YKL-40 in obesity-associated type 2 diabetes was also found (15). However, no differences in YKL-40 levels between controls and Hurley I patients may suggest the importance of skin lesions.

In the current study, AUC was 0.73 for YKL-40 and 0.72 for sIL-2R. In our previous research, AUC for sIL-2R was assessed as 0.82 (4). The results obtained in both of our studies are relatively lower than those obtained by Wieland et al. (5). However, the number of evaluated patients in our study was at least twice as high. Noteworthy, the data on sIL-2R are based on the largest number of patients until now (143 so far), and it appears to be the most reliable biomarker for differentiation between patients and healthy population. In the light of current study, YKL-40 seems to be the most sensitive biomarker for HS assessment according to Hurley staging. However, S100A8/A9 might prove to be the most valuable biomarker as the Hurley grading system may not be fully appropriate for the assessment of the severity of inflammatory processes in HS sufferers due to its static character, focusing mainly on scarification processes. The results for the sIL-2R with regard to disease severity obtained in this study are slightly inconsistent with results available in literature (4, 5).

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