Serum YKL-40 and Interleukin 6 Levels in Hodgkin Lymphoma

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Abstract

Purpose: Serum levels of the inflammatory markers YKL-40 and interleukin 6 (IL-6) are increased in many conditions, including cancers. We examined serum YKL-40 and IL-6 levels in patients with Hodgkin lymphoma, a tumor with strong immunologic reaction to relatively few tumor cells, especially in nodular sclerosis Hodgkin lymphoma.

Experimental Design: We analyzed Danish and Swedish patients with incident Hodgkin lymphoma (N = 470) and population controls from Denmark (n = 245 for YKL-40; n = 348 for IL-6). Serum YKL-40 and IL-6 levels were determined by ELISA, and log-transformed data were analyzed by linear regression, adjusting for age and sex.

Results: Serum levels of YKL-40 and IL-6 increased in Hodgkin lymphoma patients compared with controls (YKL-40, 3.6-fold; IL-6, 8.3-fold; both, $P < 0.0001$). In pretreatment samples from pretreatment Hodgkin lymphoma patients (n = 176), levels were correlated with more advanced stages (P_{trend}, 0.0001 for YKL-40 and 0.013 for IL-6) and in those with B symptoms; however, levels were similar in nodular sclerosis and mixed cellularity subtypes, by EBV status, and in younger (<45 years old) and older patients. Patients tested soon after treatment onset had significantly lower levels than pretreatment patients; however, even ≥6 months after treatment onset, serum YKL-40 and IL-6 levels remained significantly increased compared with controls. In patients who died (n = 12), pretreatment levels for YKL-40 and IL-6 were higher than in survivors, although not statistically significantly.

Conclusions: Serum YKL-40 and IL-6 levels were increased in untreated Hodgkin lymphoma patients and those with more advanced stages but did not differ significantly by Hodgkin lymphoma histology. Following treatment, serum levels were significantly lower.

Hodgkin lymphoma is a cancer with relatively few tumor cells in which the reactive response is thought to play an important role in the pathogenesis (1). Although the Hodgkin-Reed Sternberg cells seem to attract an immunologic response, that response is apparently ineffective in controlling the tumor (2). However, the higher risk for Hodgkin lymphoma and changes in the distribution of Hodgkin lymphoma subtypes in persons with immunosuppression indicate that immunity plays a role in disease incidence and histology (3). It would be of interest if circulating biomarkers of immunity correlated with either this tumor or its subtypes. YKL-40 (also called chitinase 3-like-1 protein) is one such potential biomarker, but its value in Hodgkin lymphoma has not been described. A member of mammalian chitinase-like protein family, YKL-40 is a lectin that binds heparin, chitin, and collagen and is produced by many cell types, including leukocytes and macrophages. It seems to be important in host defense mechanisms (4–6), and serum YKL-40 levels are increased in patients with diverse illnesses, including cancer. High levels have been reported in patients with primary or metastatic carcinomas, glioblastoma, melanoma, acute myeloid leukemia, and multiple myeloma and may predict recurrence and short survival (4). High serum YKL-40 levels are also found in patients with diseases characterized by inflammation, tissue remodeling, and fibrosis (5, 6).

Although its biological function in cancer is unknown, YKL-40 could play a role in proliferation and differentiation of tumor cells, angiogenesis, cell adhesion, and metastatic potential. YKL-40 could also be a marker of tissue destruction or remodeling resulting from the tumor or the vascular and immunologic reactions involved in these processes (4–6).

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Note: The results are our work, have not previously been presented, and are not under consideration elsewhere. All authors have reviewed the manuscript and concur in its presentation.

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Translational Relevance

Biological markers of cancer may help to reveal tumor pathogenesis and can serve to better define the extent of disease and prognosis. Specifically, host immune responses contribute directly to disease manifestations of Hodgkin lymphoma, including tumor mass and B symptoms. Therefore, markers related to immune response can be expected to be correlated with the presence of this disease. High serum levels of serum YKL-40 and interleukin 6 (IL-6) are nonspecific markers of inflammation and both were found to be greatly increased in pretreatment samples from Hodgkin lymphoma cases, being 4-fold and 8-fold higher than in healthy age- and sex-matched controls, respectively. Both markers were associated with B symptoms and stage, but levels did not correlate with Hodgkin lymphoma histology or EBV status. Prognosis could not be well evaluated because too few cases died during the follow-up period but likely will also be correlated with levels of these markers. Although Hodgkin lymphoma can usually be successfully managed, the levels of these markers continued to be increased at least 6 months after therapy was initiated. These and other markers should be explored for understanding the origins of B symptoms and to determine if hyperreactivity, as represented by high levels, acts as mediators or surrogate markers in Hodgkin lymphoma.

YKL-40 expression may be regulated by IL-6,[11] a cytokine produced by a variety of cells, including tumor cells, macrophages, and lymphocytes. IL-6 plays a dominant role in the immune system and the acute phase response (7), and its production is also increased in Hodgkin-Reed-Sternberg cells (1, 8–10), the neoplastic cell in Hodgkin lymphoma. We therefore examined YKL-40 and IL-6 levels in patients with Hodgkin lymphoma, hypothesizing that the levels of these two markers might correlate with the immune reaction to the malignant cells, as manifested by histology, stage, or prognosis.

Subjects and Methods

The Hodgkin lymphoma subjects were enrolled in a population-based case-control study in Sweden and Denmark. Details of the study design have been previously reported (11, 12). Briefly, the lymphoma study enrolled Hodgkin lymphoma patients with ages 18 to 74 years, diagnosed from January 1999 to mid-2002 (12). Patients with a history of organ transplantation, HIV infection, or other hematopoietic malignancies were excluded. Overall, 91% of eligible Hodgkin lymphoma patients consented to participate in the study. In the present analysis, sera obtained from 470 of 618 (76%) Hodgkin lymphoma cases were included. Stage, available on 83% of cases, was coded as Ann Arbor stages I through IV. Subjects had Hodgkin lymphoma confirmed by direct pathology review (90%) or reports of histology classified using the International Classification of Diseases for Oncology 3 codes (13). Follow-up through national population registries was truncated at death, emigration, or January 2005 (Swedes) or June 2005 (Danes), whichever came first. At enrollment, participants were asked for a blood sample and obtained pretreatment when possible. Fresh samples were sent by overnight mail for next-day processing at central laboratories in Sweden and Denmark, and the serum was stored at -80°C. Small amounts of YKL-40 and IL-6 are reported to be released into serum, probably from degranulation of neutrophils, beginning as soon as 3 h after venipuncture (14, 15). However, the amounts released would have had little impact on the high serum levels we observed in Hodgkin lymphoma patients in this study.

Serum concentrations of YKL-40 were determined by a two-site, sandwich-type ELISA (16) in accordance with the manufacturer's instructions (Quidel[12]). The sensitivity of the ELISA for serum YKL-40 was 20 ng/mL, and the intra-assay and interassay coefficients of variation were ≤5.0% and ≤10.2%, respectively (14). Serum concentrations of IL-6 were measured by ELISA (R&D Systems) in accordance with the manufacturer's instructions. The sensitivity of the ELISA for serum IL-6 was 0.01 pg/mL, and the intra-assay and interassay coefficients of variation for IL-6 were ≤10.5% and ≤17.7%, respectively (15). For reference, serum YKL-40 and serum IL-6 were determined in apparently healthy Danish adult volunteers (blood donors and residents of retirement homes) from 18 to 79 years, who were not on medication, as previously described (14, 15). Measurements of serum YKL-40 and IL-6 concentrations in Hodgkin lymphoma patients were done in the same laboratory using the same assay as for the normal sera panel.

We used linear regression on the log-transformed concentration measurements to determine the associations of various factors with serum YKL-40 and IL-6 concentrations. We modeled deviation from the expected concentration level in age- and sex-matched healthy persons, obtained by linear regression of age and sex on the log-transformed concentration measurements in the normal sera samples. For YKL-40 and IL-6 associations with survival, estimated by Cox regression analysis, the entry was at the date of blood sampling. Confidence intervals and two-sided significance tests were based on Wald tests.

Results

Levels in healthy individuals (n = 245 for YKL-40; n = 348 for IL-6) are presented in Fig. 1. We used serum levels estimated in 35-year-old healthy women as the reference value for statistical comparisons, 35 years being the median age of the Hodgkin lymphoma cases. For YKL-40, this baseline serum level was 39 ng/mL. Serum YKL-40 levels increased by a factor of 1.15 per decade of age [95% confidence interval (95% CI), 1.12-1.19; $P_{trend} \leq 0.0001$], and the age-adjusted median level was lower in males than in females by a factor of 0.91 (95% CI, 0.82-1.04). For serum IL-6, the baseline level was 1.3 pg/mL and levels increased by a factor of 1.07 per decade of age (95% CI, 1.00-1.15; P_{trend} = 0.07). After age adjustment, serum IL-6 levels in males were higher than in females by a factor of 1.15 (95% CI, 0.98-1.34).

The characteristics of the 470 Hodgkin lymphoma patients in the present study are provided in Table 1. Males and females were equally represented and the bimodal age distribution was typical of Hodgkin lymphoma, as was the predominance (69%) of nodular sclerosis Hodgkin lymphoma. For 388 patients, stage was known. For 98 patients, treatment status at the time of blood collection was not certain. The age, sex, and histology distributions did not differ between cases with and without known treatment status; however, YKL-40 and IL-6 levels were similar to those in treated patients, suggesting that most of those without treatment information had been treated (data not presented).

[11] J.S. Johansen, personal observation.

[12] Quidel had no role in (*a*) the design of the study, (*b*) the data collection, analysis, and interpretation, and (*c*) the preparation of the manuscript, and had no rights to approve, delay, or disapprove of publication of the work.

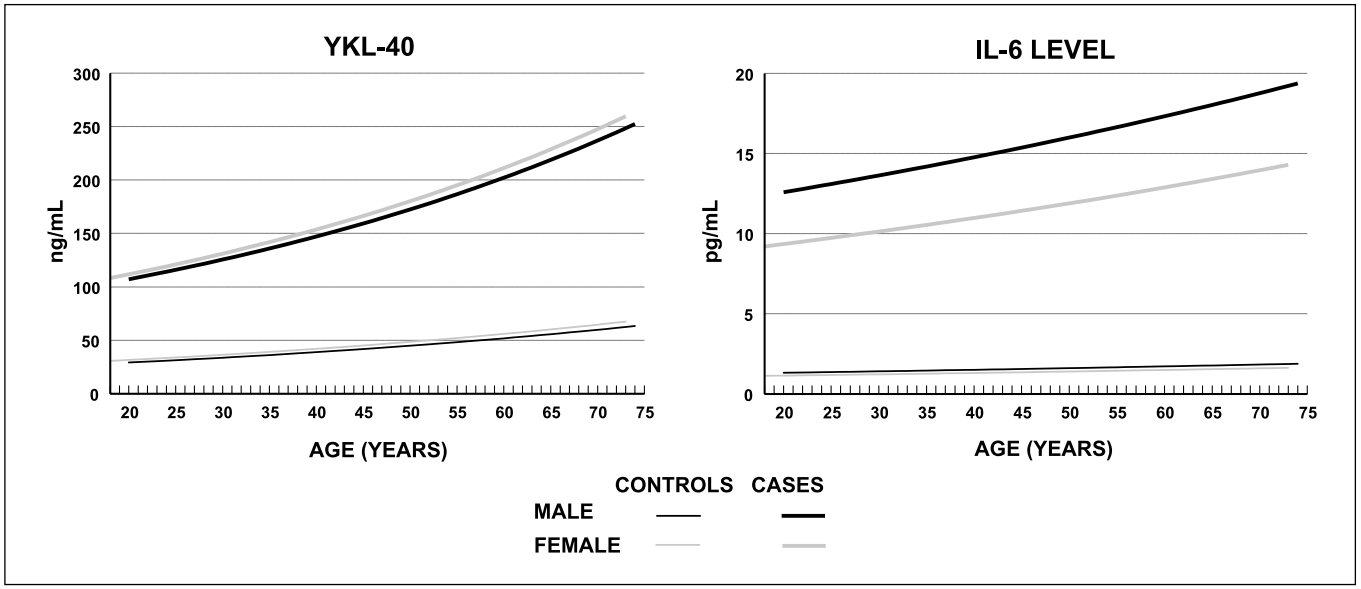

Fig. 1. Modeled levels of YKL-40 and IL-6 in cases and controls, by sex.

Among 176 Hodgkin lymphoma patients with pretreatment samples, age- and sex-adjusted serum levels of YKL-40 and IL-6 were significantly higher than in healthy persons at all ages [overall relative values (95% CI): YKL-40, 3.6 (3.1-4.2); IL-6, 8.3 (5.94-11.7); Fig. 1]. Relative serum levels of YKL-40 and IL-6 were not significantly different in 67 younger (<45 years old) versus 129 older Hodgkin lymphoma patients ($P = 0.86$ and $P = 0.30$, respectively), and the two groups were therefore combined for analysis. YKL-40 and IL-6 were moderately correlated ($r = 0.31$; $P < 0.0001$) with each other. After adjustment for age and sex, median serum levels of YKL-40 levels were 3.7-fold higher in patients with nodular sclerosis Hodgkin lymphoma (95% CI, 3.1-4.5) and 3.1-fold higher in patients with mixed cellularity Hodgkin lymphoma (95% CI, 1.9-5.1) compared with the normal subjects. Similarly, serum IL-6 levels were increased 9.0-fold in nodular sclerosis Hodgkin lymphoma (95% CI, 6.3-12.9) and 8.4-fold for mixed cellularity Hodgkin lymphoma (95% CI, 3.3-21.6). Other specified Hodgkin lymphoma subtypes occurred too infrequently to allow robust comparisons. Patients with mixed cellularity Hodgkin lymphoma were older and more likely to be male than nodular sclerosis Hodgkin lymphoma patients. After adjusting for the age and sex difference, serum YKL-40 and IL-6 levels did not differ significantly between nodular sclerosis

Table 1. Characteristics of 470 Hodgkin lymphoma cases diagnosed between 1999 and 2002 and examined for serum YKL-40 and IL-6

Stratum	Treatment status (*n*)			
	All	Pre-onset	After onset	Unknown
Total	470 (100%)	176 (100%)	196 (100%)	98 (100%)
Country of residence				
Sweden	288 (61%)	121 (69%)	109 (56%)	58 (59%)
Denmark	182 (39%)	55 (31%)	87 (44%)	40 (41%)
Sex				
Male	245 (48%)	102 (48%)	94 (48%)	49 (50%)
Female	225 (52%)	74 (52%)	102 (52%)	49 (50%)
Age [y; median (25-75%)]	35 (27-54)	35 (27-54)	35 (26-54)	38 (29-54)
HL histology				
Nodular sclerosis	326 (69%)	116 (66%)	148 (75%)	62 (63%)
Mixed cellularity	86 (18%)	37 (21%)	31 (16%)	18 (18%)
Other/undefined	58 (12%)	23 (13%)	17 (9%)	18 (18%)
HL stage (Ann Arbor)				
I	74 (16%)	32 (18%)	34 (17%)	8 (8%)
II	187 (40%)	82 (47%)	74 (38%)	31 (32%)
III	84 (18%)	34 (19%)	40 (20%)	10 (10%)
IV	43 (9%)	18 (10%)	16 (8%)	9 (9%)
Missing	82 (18%)	10 (6%)	32 (16%)	40 (41%)

Abbreviation: HL, Hodgkin lymphoma.

and mixed cellularity Hodgkin lymphoma in pretreatment samples (P, 0.86 and 0.37, respectively).

Pretreatment serum levels were higher in patients with more advanced disease stages (P_{trend} YKL-40 = 0.0001 and P_{trend} IL-6 = 0.013; Table 2). Data about B symptoms were available only for Danish patients. Of 55 subjects with pretreatment samples and data, 18 (33%) had B symptoms. Relative serum YKL-40 levels were higher in patients with B symptoms (1.8; 95% CI, 1.3-2.3) than those without B symptoms. IL-6 levels were also higher in patients with B symptoms than those without B symptoms, although the difference was not statistically significant (1.3; 95% CI, 0.5-3.0). The 38 patients with EBV-positive tumors had marginally lower serum YKL-40 levels (median relative level, 0.8; 95% CI, 0.6-1.0) but marginally higher serum IL-6 levels (1.3; 95% CI, 0.7-2.2) than 125 patients with EBV-negative tumors after adjustment for age and sex.

In 196 samples obtained after treatment onset, serum levels of YKL-40 and IL-6 were also modestly correlated (r = 0.27; P = 0.001). The timing of the sample collection varied among the 196 patients with serum obtained after therapy had started. Serum levels of YKL-40 were lower in treated patients, even when the treatment had only been recently started, being 61%, 56%, and 70% of the pretreatment levels at 0 to 2 (n = 98), 3 to 5 (n = 21), and ≥6 months (n = 29) after therapy onset, respectively. Correspondingly, IL-6 levels were 66%, 42%, and 47% of pretreatment levels at 0 to 2, 3 to 5, and ≥6 months, respectively (Table 2). Overall, serum levels ≥6 months after treatment onset were lower than in pretreatment samples (P = 0.007 for YKL-40 and P < 0.01 for IL-6), but they remained 2.5-fold (95% CI, 1.8-3.5; P < 0.0001) higher for YKL-40 and 2.2-fold (95% CI, 1.0-5.1; P = 0.06) higher for IL-6 than levels in healthy subjects.

Twelve Hodgkin lymphoma patients with pretreatment samples had died by the end of follow-up in 2005, including 11 with nodular sclerosis Hodgkin lymphoma. Although serum YKL-40 and IL-6 levels were higher in nodular sclerosis Hodgkin lymphoma patients who died than in survivors with nodular sclerosis Hodgkin lymphoma, the differences were not statistically significant. The hazard ratios for death were 1.58 (95% CI, 0.75-3.33) for serum YKL-40 and 1.12 (0.75-1.66) for serum IL-6 per log unit change. Twelve additional subjects with samples collected after treatment onset died, and, in them, serum levels of YKL-40 and IL-6, although higher than in survivors, were also not statistically significant predictors of prognosis.

Discussion

Compared with healthy subjects, serum levels of YKL-40 and IL-6 were high in pretreatment samples of patients with nodular sclerosis and mixed cellularity Hodgkin lymphoma. In patients with Hodgkin lymphoma, pretreatment serum levels of YKL-40 and IL-6 were correlated directly with disease stage and presence of B symptoms (YKL-40 only) but similarly increased in patients who were younger (<45 years) versus older at onset, had nodular sclerosis and mixed cellularity Hodgkin lymphoma subtypes, and with EBV-positive versus EBV-negative tumors. In treated patients, serum YKL-40 and IL-6 levels were significantly lower than in pretreatment patients, but both levels still remained significantly higher than in healthy controls, even ≥6 months after therapy onset. Although levels were not significantly correlated with prognosis, we had limited power to evaluate prognosis because few people died during the follow-up period of this study.

Table 2. Age- and sex-adjusted relative levels of serum YKL-40 and IL-6 in healthy subjects (n = 245 for YKL-40 and n = 348 for IL-6) and patients with pretreatment (n = 176) and treated (n = 29) Hodgkin lymphoma

	YKL-40	IL-6
Healthy controls		
Increase per decade	1.15 (1.12-1.19)	1.07 (1.00-1.15)
Males compared with females	0.92 (0.82-1.04)	1.15 (0.98-1.34)
Relative serum levels in pretreatment patients with HL compared with healthy controls*		
Overall HL	3.63 (3.10-4.24)	8.32 (5.94-11.7)
Histology		
Nodular sclerosis	3.73 (3.13-4.46)	9.00 (6.26-12.9)
Mixed cellularity	3.15 (1.93-5.14)	8.42 (3.28-21.6)
Other/undefined	3.40 (2.32-4.98)	6.06 (1.91-19.2)
Ann Arbor stage		
I	3.42 (2.35-4.98)	8.28 (2.60-26.4)
II	3.28 (2.74-3.92)	5.95 (3.91-9.06)
III	4.23 (2.89-6.20)	14.97 (7.28-30.8)
IV	4.20 (2.24-7.90)	20.42 (6.58-63.4)
	P_{trend} < 0.0001	P_{trend} = 0.013
Serum level ≥6 months after treatment onset compared with pretreatment level (%) †		
Overall HL	70 (53-91)	47 (26-83)
Nodular sclerosis	69 (50-95)	30 (15-58)
Mixed cellularity	79 (44-141)	98 (33-291)
Other/undefined	52 (24-113)	112 (11-1152)

NOTE: For reference, relative levels were compared with serum levels estimated for healthy 35-year-old women: 39 ng/mL for YKL-40 and 1.3 pg/mL for IL-6.

*Relative to age- and sex-adjusted levels in healthy controls.

† Difference relative to median serum levels in untreated patients after age and sex adjustment. For example, in Hodgkin lymphoma patients, median levels for YKL-40 were 70% of those seen in pretreatment patients after age and sex adjustment.

The pathology and clinical symptoms of Hodgkin lymphoma involve a complex interplay of chemokines and cytokines derived from both the Hodgkin-Reed-Sternberg cells and the surrounding reactive cells (1). This reactivity seems to involve the immune system (2, 3). Only a small percentage of the tumor mass in Hodgkin lymphoma is composed of neoplastic cells and most of the mass is created by the immunologic reaction surrounding the tumor cells (2). The higher serum levels of YKL-40 might be mediated by tumor cells expressing IL-6 (known to be produced excessively by Hodgkin-Reed-Sternberg cells and the surrounding reactive cells; refs. 1, 8–10), by the immunologic reaction induced by these cells (2, 13), or by tissue destruction and remodeling related to the tumor mass. A reasonably intact immune system seems to be essential for the manifestation of the sclerosing reaction characteristic of nodular sclerosis Hodgkin lymphoma because it is not seen in persons who are profoundly immunosuppressed (3). In contrast, patients with mixed cellularity Hodgkin lymphoma may have less immunologic reaction to their tumors. Because YKL-40 and IL-6 levels were similar in nodular sclerosis and mixed cellularity Hodgkin lymphoma, after adjustment for age and sex, we speculate that the differences in the immune responses to Hodgkin-Reed-Sternberg cells are not driving YKL-40 or IL-6 production. Rather, cytokine signals from the malignant cells or tissue damage from the tumor mass (including the immunologic reaction to it) may be more important triggers. However, IL-6 levels were found to be increased in the unaffected identical twin mates of persons with Hodgkin lymphoma, leading those authors to suggest that IL-6 response may be a marker of susceptibility to Hodgkin lymphoma (10).

Compared with pretreatment samples, the average serum levels of YKL-40 and especially IL-6 were lower in patients whose samples were obtained within weeks after therapy onset, possibly reflecting a rapid response to therapy. However, even ≥6 months after therapy onset, serum levels of YKL-40 and IL-6 remained higher than in healthy persons. In treated patients, most samples would have been collected while they were still on therapy; thus, the declines may have been due either to clearing of tumor tissue or to therapy itself, such as by its effect on immunocytes or other cells. Consistent with studies in other cancer types (4, 5, 7), serum YKL-40 and IL-6 levels in pretreatment samples correlated with disease burden, as measured by stage, and were higher in individuals who later died than in survivors. However, few of these patients died during follow-up, and we cannot be confident about the relationship between level and survival. In addition, we were not able to identify whether deaths were related to therapy, disease progression, or other reasons.

In summary, we found that serum levels of YKL-40 and IL-6 are higher in pretreatment Hodgkin lymphoma cases than in healthy controls and in patients with more advanced stages of Hodgkin lymphoma, but they were similar in nodular sclerosis and mixed cellularity Hodgkin lymphoma. Further work will be needed to determine whether these proteins act as direct mediators or surrogate markers of the disease process in Hodgkin lymphoma.

Disclosure of Potential Conflicts of Interest

The authors have no conflict of interest in any aspect of this article.

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