Role of High-sensitivity C-reactive Protein in the Differentiation of Benign and Malignant Soft Tissue Tumors

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Abstract. *The aim of the present study was to determine whether serum high-sensitivity CRP (hs-CRP) levels can be used to predict the differentiation of benign soft tissue tumors and soft tissue sarcomas (STS) and whether there are any links between increased hs-CRP levels and patients' characteristics. Serum samples were collected from 14 healthy subjects, 35 patients with benign soft tissue tumors and 60 patients with STS. The Hs-CRP levels in the patients with STS were statistically higher than those observed in patients with benign soft tissue tumors ($p<0.0001$) and control subjects ($p<0.0001$). There were no significant differences in the hs-CRP levels between patients with benign soft tissue tumors and control subjects ($p=0.16$). In the receiver operating characteristic analysis, a value of 0.95 μg/ml was found to be an appropriate threshold for identifying patients at-risk for STS. The area under the curve was 0.747. The serum hs-CRP level exhibited a sensitivity and specificity STS of 50% and 94.3%, respectively, for identifying. The current analyses showed that an elevated hs-CRP level is associated with the presence of STS and may, therefore, be used as an additional marker for the differential diagnosis of soft tissue tumors.*

Recent studies have suggested that an elevated C-reactive protein (CRP) level is a poor prognostic factor in patients with soft tissue sarcoma (STS) (1-3). We previously reported, however, that a CRP level above the normal is observed in only 18% of patients with histological grade 1-3 STS (2). The high-sensitivity C-reactive protein (hs-CRP) level is a frequently used marker of inflammation. The level of Hs-CRP can be used to accurately measure for a low level of CRP. Elevated hs-CRP levels have been reported in patients with many diseases, including cardiovascular disease, diabetes, metabolic syndrome and several types of cancers (4, 5). Although the level of CRP may be within the normal range in most patients with soft tissue tumors, it is possible that the hs-CRP levels are higher in STS patients than in those with benign soft tissue tumors and healthy subjects and may, therefore, be a useful marker for differentiating benign soft tissue tumors from STS. The aim of the present study was to determine whether serum hs-CRP levels can be used to predict the differentiation of benign soft tissue tumors and STS and whether there are any links between increased hs-CRP levels and patients' characteristics.

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Key Words: High-sensitivity C-reactive protein, soft tissue tumor, biomarker, diagnosis.

Patients and Methods

Serum samples were collected from 14 healthy subjects, 35 patients with benign soft tissue tumors and 60 patients with STS. Patients who presented with local recurrence or/and metastasis at presentation or who were referred for additional resection after undergoing previous inadvertent excision were excluded from the study. The patients with obvious history of cardiac infarction or infectious disease were also excluded from this study. The histopathological diagnosis and tumor grade were determined using the French Federation of Cancer Centers Sarcoma Group (FNCLCC) system were reviewed in all patients and confirmed by independent pathologists. The blood samples were obtained prior to initial treatment in all patients and measured using the CircuLex™ hs-CRP ELISA kit (Nagano, Japan) followed by centrifugation at 3,000 × *g* for 10 min. All sera were stored at –80˚C until measurement. All samples were collected under the approval of the ethics committee of our Institution.

The primary purpose of this study was to determine whether the serum hs-CRP level can be used to predict the differentiation of benign soft tissue tumors from STS. Further aims were to investigate whether there are any links between an increased hs-CRP level and patients' characteristics, including age, gender, body-mass index (BMI), tumor size, tumor depth and histology.

Statistical analysis. Statistical associations between clinicopathological factors were evaluated using the Mann-Whitney *U*-test and Kruskal Wallis test for quantitative data and the Chi-square test for qualitative data. Correlations between the hs-CRP levels and clinical characteristics

Table I. *Patients' and control subject characteristics.*

Variables	STS (n=60)	Benign tumors (n=35)	Controls (n=14)
Age (years)			
Mean	64	44	42
Gender			
Male	34	15	6
Female	26	20	8
Hs-CRP (μg/ml)			
Mean	3.31	0.47	0.73
Median	0.95	0.38	0.57

STS; Soft tissue sarcoma. Hs-CRP; High-sensitivity C-reactive protein.

were tested using a Spearman rank correlation analysis. A significant Spearman ϱ implied a correlation in the population. A value of $p<0.05$ was considered to be significant in all statistical analyses. A receiver operating characteristic (ROC) analysis was performed to determine the threshold of the hs-CRP level for the risk of STS.

Results

Patient, tumor and control subject characteristics. Details of the clinicopathological features of the 95 patients with soft tissue tumors are listed in Tables I and II. The patients comprised of 49 males and 46 females, with a mean age of 56 (range=10-89) years at first presentation. The mean body-mass index (BMI) was 22.9. There were 35 benign tumors, including 10 lipomas, nine fibromatoses, six schwannomas, three hemangiomas, three neurofibromas and four other tumors. There were also 60 soft tissue sarcomas, including 15 well-differentiated liposarcomas, 12 undifferentiated pleomorphic sarcoma/malignant fibrous histiocytomas, eight myxofibrosarcomas, seven leiomyosarcomas, five malignant peripheral nerve sheath tumors, three myxoid liposarcomas, two de-differentiated liposarcomas, two dermatofibrosarcoma protuberances and six other high-grade sarcomas. The histological grade of soft tissue sarcoma was low in 18 sarcomas and high in 42 sarcomas.

The control subjects comprised of six males and eight females. The mean age of the control subjects was 42 (range=23-69) years (Table I). All control subjects were healthy volunteers without any medical history of cancer and cardiovascular disease.

Serum hs-CRP levels in the patients with soft tissue tumors and control subjects. The patients with STS were significantly older than those with benign soft tissue tumors and control subjects ($p<0.0001$). Age exhibited a weak-to-low correlation (Spearman ϱ=0.376, $p<0.0001$) with the hs-CRP level based on the Spearman rank correlation in all subject including 95 patients and 14 healthy control (Figure 1).

Table II. *Clinical characteristic in patients with 95 soft tissue tumors.*

Variables	Patients with benign tumors	Patients with STS
Mean age (years)	44	64
Gender		
Male	15	34
Female	20	26
Tumor depth		
Superficial	6	13
Deep	29	47
Tumor size		
Mean (cm)	6	10
≥5 cm	19	46
<5 cm	16	14
Mean BMI	22.5	23.1

STS; Soft tissue sarcoma. BMI; Body-mass index.

Table III. *a. The association between hs-CRP and patients characteristics in soft tissue tumors.*

Variables	n	Mean levels of hs -CRP (μg/ml)	*p*-Value
Gender			
Male	49	2.43	0.17
Female	46	2.09	
Tumor depth			
Superficial	19	1.49	0.8
Deep	76	2.46	
Tumor size			
≥5 cm	65	2.61	0.04
<5 cm	30	1.52	
Tumor diagnosis			
Benign	35	0.47	<0.0001
Malignant	60	3.31	

hs-CRP; High-sensitivity C-reactive protein.

b. Correlation of hs-CRP with clinical variables.

Variables	Spearman ϱ	*p*-Value
Increasing age	0.353	0.0006
Larger BMI	0.047	0.66

hs-CRP; High-sensitivity C-reactive protein. BMI; Body-mass index.

The median serum hs-CRP level was 0.95 μg/ml (range=0-16.5, mean=3.31) μg/ml in patients with STS, 0.38 (range=0-2.57, mean=0.47) μg/ml in the patients with benign soft tissue tumors and 0.57 (range=0-2.53, mean=0.73) μg/ml in the control subjects. The Hs-CRP levels in the patients with STS were statistically higher than those

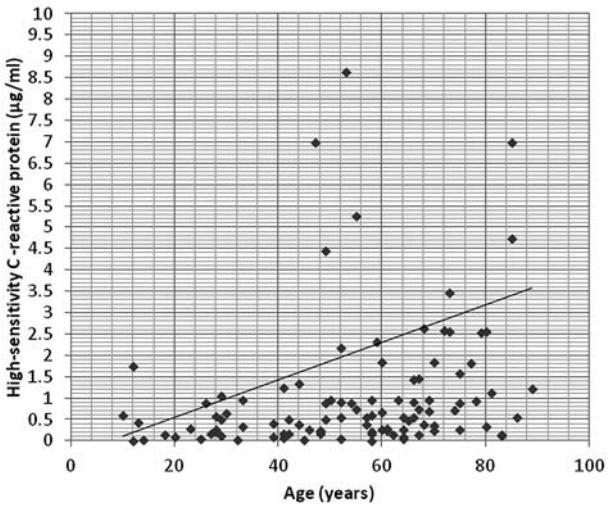

Figure 1. *Correlation between the hs-CRP level and age. The Hs-CRP level exhibited a significantly weak-to-low correlation with age (Spearman ϱ=0.376, p<0.0001).*

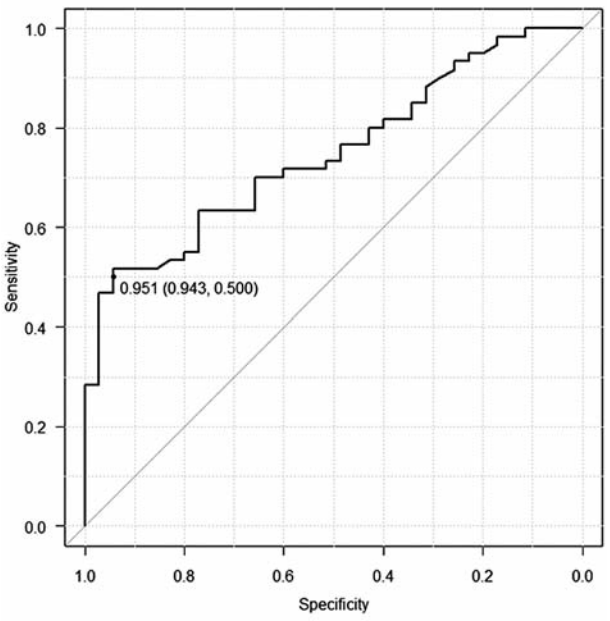

Figure 2. *ROC curve showing the appropriate threshold of the hs-CRP level for identifying soft tissue tumor patients at risk of developing STS.*

observed in the patients with benign soft tissue tumors ($p<0.0001$) and control subjects ($p<0.0001$). There were no significant differences in hs-CRP levels between patients with benign soft tissue tumors and control subjects ($p=0.16$).

Associations between serum hs-CRP levels and clinicopathological variables in patients with soft tissue tumors. The associations between serum hs-CRP levels and clinicopathological variables in patients with soft tissue tumors are shown in Table III. The patients with tumors 5 cm or larger in size had higher serum hs-CRP levels than those with tumors smaller than 5 cm in size ($p=0.04$). Age exhibited a weak-to-low correlation (Spearman ϱ=0.353, $p=0.0006$) with hs-CRP levels based on the Spearman rank correlation. The Hs-CRP levels in patients with STS were statistically higher than those observed in patients with benign soft tissue tumors ($p<0.0001$). In the ROC analysis, a value of 0.95 μg/ml was found to be an appropriate threshold for identifying patients at-risk for the development of STS. The area under the curve (AUC) was 0.747 (95% confidential interval; 0.651-0.844) (Figure 2). An elevated hs-CRP level (>0.95 μg/ml) was observed in 30 out of 60 patients with STS and two of 35 patients with benign soft tissue tumors. The serum hs-CRP level exhibited a sensitivity and specificity for identifying STS of 50% and 94.3%, respectively.

The level of serum hs-CRP was not found to be associated with BMI, based on the Spearman rank correlation (Spearman ϱ=0.047, $p=0.66$). Specifically, there were no differences in the hs-CRP levels between patients with lipoma and those with well-differentiated liposarcoma ($p=0.78$). Next, when we analyzed the 30 patients with <5cm soft tissue tumors, the hs-CRP levels in patients with STS (median, 1.26 μg/ml) had significantly higher than those with benign soft tissue tumors (median, 0.24 μg/ml) ($p=0.01$). Among the 60 STS patients, the patients with high-grade tumors had higher hs-CRP levels than those with low-grade tumors ($p=0.04$).

Discussion

Magnetic resonance imaging (MRI) and computed tomography (CT) remain important modalities for evaluating soft tissue masses (6). Although some lesions can be readily-identified based on their imaging characteristics, many soft tissue tumors remain indeterminate and require a biopsy for diagnosis of the histology and tumor grade (6). The identification of additional differential diagnostic markers that are accurate and readily-available has the potential to ease the clinical management of patients with soft tissue tumors. Current analyses showed that an elevated hs-CRP level is associated with the presence of STS and may therefore be used as an additional marker for the differential diagnosis of soft tissue tumors. No studies have thus far revealed the diagnostic value of the hs-CRP levels in patients with soft tissue tumors. Furthermore, patients with high-grade tumors have higher hs-CRP levels than those with low-grade tumors. These results suggest that an elevated hs-CRP level possibly reflects aggressive characteristics. Several possible mechanisms have been suggested to explain the relationships

between malignant tumors and inflammatory markers, such as the levels of hs-CRP and CRP. One possible mechanism is that tumor growth induces inflammation around the tumor (7). Alternatively, cancer cells may increase the production of inflammatory proteins (8-10). Specifically, in this study, there were no differences in the hs-CRP levels between patients with lipoma and those with well-differentiated liposarcoma. The present analysis may have been affected by the fact that well-differentiated liposarcoma is usually slow-growing and exhibits a good prognosis. Furthermore, our cohort did not include patients with retroperitoneal liposarcoma, which sometimes develops local recurrence or de-differentiation (11). Interestingly, we found the level of hs-CRP in patients with small (<5 cm) STS to be significantly higher than those with small benign soft tissue tumors. Most unplanned excisions are performed on patients with relatively smaller and more superficial tumors, many times with or without advanced imaging. We believe that the measurement of hs-CRP may be helpful especially for smaller tumors to distinguish STS from benign soft tissue tumors.

There are a few limitations to the present study. First, the presence of other diseases may be associated with an elevated hs-CRP level. Although we found that age was weakly-associated and BMI was not associated with the hs-CRP level, other medical conditions were not taken into consideration due to lack of information. Furthermore, soft tissue tumors have a variety of pathological classifications, and we were only able to investigate a few samples for each histology due to the rarity of the disease. Only identifies 50% of known malignant soft tissue masses were not very helpful. However, 94% specificity was fine and we believe that the measurement of hs-CRP may be useful especially for smaller soft tissue tumors to distinguish benign from malignant soft tissue tumors.

In conclusion, we found that the serum hs-CRP level is associated with the presence of STS. The Hs-CRP level can be used as diagnostic tool in the differentiation of benign and malignant soft tissue tumors in addition to imaging examinations.

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