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Circulating serum C- reactive protein: a prognostic marker in naive patients with cancer at the Yaounde General Hospital

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Abstract

In Cameroon, the main determinant of cancer mortality is the advanced stage at the time of diagnosis. The purpose of this work is to determine the relationship between C-reactive Protein (CRP) concentration and advanced cancer stage. This is a cross-sectional study conducted at Yaoundé General Hospital. 276 naive patients with histological evidence of cancer were included in this study. Serum CRP level was correlated with the specific characteristics of the tumor. The study population was made of 74% women and 26% men with a minimum age of 22 years and a maximum age of 80 with an average age of 46 years. The cancer type with the highest prevalence was breast cancer (43.5%), followed by Kaposi's sarcoma (8.7%), Non Hodgkin Lymphoma (8.7%), CRP values were Classified into two groups based on pathological values (CRP≥ 6 mg/l) and non-pathological values (CRP <6 mg/l). The elevated CRP concentration was not significantly associated with the presence of metastasis M (P = 0.074), T-cancer stage (P = 0.09), N-lymph nodes (P = 0.111), advanced histological grade G-3 (P = 0.115) and cancer type (P = 0.124). Our study shows that elevated serum CRP is not a marker of cancer extension.

Keywords: CRP, cancer, inflammation, prognostic.

Introduction

Inflammation is the response of vascularized tissues to aggression (microorganism, trauma, ischemia). It has several roles: natural defense and repair of injured tissues [1]. It can have several causes: stress, environmental pollutants, viruses, bacteria and food [2].

Inflammation can occur biologically by the decrease of certain markers, namely albumin, ferritin and by the increase of other markers such as: serum amyloid A (SAA), CRP (protein-C reactive) [3]. However, inflammation in the cancerous process could be materialized by increase in certain serum proteins, including CRP. Therefore, it has been shown that a high level of CRP can be used as a predictive marker for metastases in penile cancers [3]. Similarly, studies have shown that a high level of CRP can be used as a prognostic marker of poor survival [4]. In addition, the first marker of poor survival in patients with cancer was advanced stage [5]. This advanced stage, which is 95% at the time of diagnosis, is the main determinant of high mortality due to cancer [6]. Methods for

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evaluating the spread of cancer, including medical imaging, are very expensive and still have limits because their resolotion is on average 10 millimeters, which is equivalent to a nodule of one billion cells which could go unnoticed at the time of diagnosis[7]. Then the study consisted of showing whether there might be a relationship between biological markers (CRPs) and the extension of cancer.

Material and methods

We carried out a cross-sectional study at the Yaoundé General Hospital, the Oncology Service and the Laboratory.The studylasted over a period of 10 months, from March to December 2014. None of our patients had initiated chemotherapy. The study was approved by the Institutional Committee of Ethics of Research for Human Health of the UCAC School of Health Sciences. We had 69 patients by a consecutive non-probabilistic sampling recruited during consultations and meeting the criteria of inclusion of age 21 years and older; patients with histologically proven cancer, people with an extension report including at least: chest x-ray and pelvic ultrasound, Clinical examination (tumor examination ie finding any superficial ganglion and lesion that may notice Kaposi's Sarcoma) and patients who had not yet received treatment. Due to the small sample size, werecruited 207 patients coming from a cohort study from 2015 to 2017. We took these patients because they had the same features with the first group of population and they had all the information needed. patients who had cancer in addition to other diseases were recruited and this factor was taken into account in the statistical analysis. Metastasis nodules were determined by medical imaging techniques (scanner, MRI). The histological parameters of the extension were determined by the pathological examinations and classified according to the TNM 2002 classification. The information obtained from the patient from a standardized questionnaire were classified in socio-demographic characteristics such as sex, age. Then in clinical characters: size, weight, types of cancer, primary tumor diameter, presence of ganglion, number and localization, presence of inflammatory syndrome, presence of metastases, number and localization; in anatomopathological parameters, grade and stage; biological characteristics: CRP and NFS. The CRP value was split into two (<6 mg / l and ≥ 6mg / l) according to the suggestion of Saito et al., 2007 and according to our context where a CRP value ≥ 6mg / l is pathological.

Statistics

Continuous variables were reported as mean value and standard deviation (SD) or median value and interquartile ranges (IQR) in the case of parametric or non-parametric distribution, respectively. Chi2 and Fisher's exact tests were conducted to assess correlations of nominal covariate distributions and CRP-groups. The t-test (in case of parametric) was applied to compare metric variables between two or more subgroups. SPSS 20.0 was used for statistical assessment. In all tests, a two-sided $p<0.05$ was considered to indicate significance.

Results

Our patient population with an available pre-treatment CRP value consisted of 72 (26.1%) men and 204 (73.9%) women had a mean (median) age of 50.17 (46) years (22-80). The median body mass index (BMI) for all patients was 27.61 kg/m2 (IQR, 23.07 –30.12). Breast cancer was the most represented with 43.5%, followed by Kaposi sarcoma (8.7%), NHL (8.7%), cervix cancer (7.2%), prostate cancer and multiple myeloma have respectively 4.2% and others cancers (22%) includingmalignant melanoma, lymphangitis, malignant hemangioendothelium, adrenal cancer, ovarian cancer, vaginal cancer, placenta cancer, pancreatic cancer, liver cancer, cavum cancer, colon cancer, thyroid cancer, esophagus and bronchial cancer in figure 1. Detailed patients' and tumour characteristics including stage and grade are summarized in Table 1 and Table2.

The mean pre-treatment CRP value of all 276 evaluable patients was 35.84 (12.0) mg/l. The mean CRP value in the two subgroups was 5.00(4.04) and 31.00 (55.07) mg/l, respectively. Both groups were comparable concerning the distribution of sexes ($p=0.016$; Fisher's exact test, Table 1), the BMI value ($p=0.221$; t-test) and tumour location ($p=0.124$, Fisher's exact test; Table 2) as well as age, patients with a CRP <6mg/l tended to be older ($p=0.47$; t-test) Table 1.

The CRP-level was not correlated significantly with the tumour stage: 24.64 and 42.03% of all patients with a CRP<6 and ≥ 6mg/l,suffered from invasive disease (pT≥3) at the time diagnosis ($p<0.51$, Fisher's exact test). Accordingly, the median CRP value was not significantly lower in those patients with superficial compared to invasive cancer (9.0 vs. 12.0 mg/l; $p<0.253$, t-test). The risk of presenting nodal disease ($p=0,111$, Fisher's exact test, Table 2) was not increased significantly as comparedto distant metastasis ($p=0,074$, Fisher's exact test; Table 2) in patients with a CRP value ≥ 6mg/l. Moreover, elevated CRP-levels were found in 18.42, 10.52 and 26.31% of

patients with G1, G2 and G3 tumours, respectively (p<0,115, Chi2 test, Table 2).

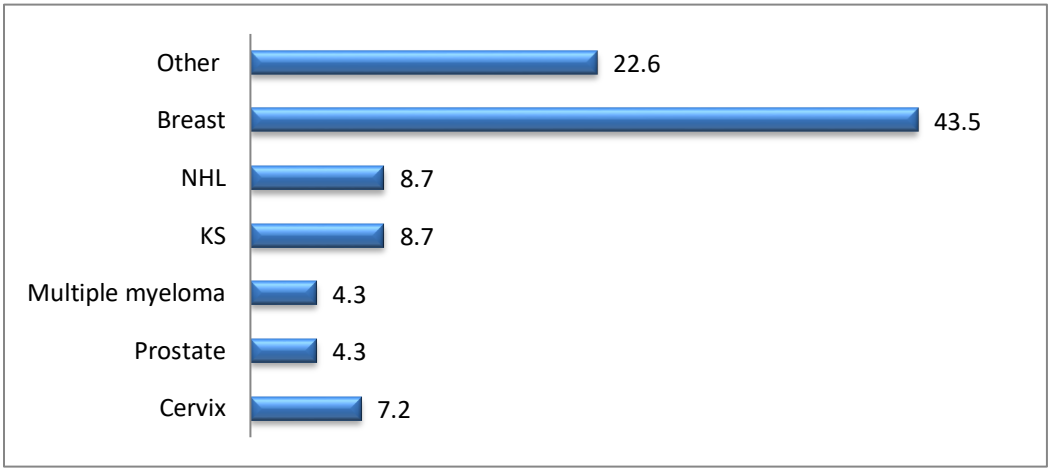

Fig.1: Distribution of the study population according to the type of tumor

Table 1 : Characteristics of the population

Variables	CRP<6(%)	CRP≥6(%)	P-value	Tests
Age, mean(Years)±SD	51,54 ±(15,467)	49,35±(9,584)	0,470	t-test
BMI, mean(Kg/m^2) ±SD	27,36±(5,73)	23,93±(5,17)	0.221	t-test
Sexe			0,097	Fisher
F	88(31.88)	116(42.03)		
M	16(5.79)	56(20.29)		

Table 2: Clincal

Variables	CRP<6(%)	CRP≥6(%)	P-value	Tests
Types de cancers			0.124	Fisher
Breast Cancer	64(53,3)	56(46,7)		
Others cancers	40(25,7)	116(74,3)		
Metastasis			0,074	Fisher
M+	4(25)	72(27, 7)		
M-	12(75)	188(72, 3)		
Lymph node			0,111	Fisher
N+	60(50)	60(50)		
N-	44(30,6)	100(69, 4)		
Leucocytes			0,033	Chi-square
<4000	28(58,3)	20(41,7)		
4000-10000	56(42,4)	76(57,6)		
>10000	4(8,3)	44(91,7)		
Stade			0.09	Fisher
≤ T-2	32(45,5)	40(55,5)		
≥ T-3	68(37,8)	112(62,2)		
Grade			0,115	Chi-square
G1	20(13.15)	28(26.32)		

G-2	24(15.78)	16(10.52)		
G-3	24(37,5)	40(62,5)		

Discussion

CRP is an essential biomarker of the inflammatory response. Several studies have indicated that serum CRP levels are an independent predictor of prognosis for various solid tumors, HL, and NHL [8, 9] . However, the prognostic role of serum CRP levels in many cancers taken on the same time remains unclear. The distinct characteristics of prominent regional necrosis and inflammation observed in cancer patients prompted us to analyze the impact of CRP on the prognostic outcome of patients with cancer. To the best of our knowledge, the present study represents the largest series and the first one to date examining the prognostic value of serum CRP levels in several types of cancer at the same time. Our study aimed to show the association between CRP levels and the extension of cancers. Like the study titled "Preoperative serum C-reactive protein: a prognostic marker in patients with urothelial carcinoma", she addressed the relationship between CRP and cancer extension. It took into account the extension in the three categories TNM (stage T, lymph node and metastasis) thus allowing a more holistic approach to the extension of the tumor. It appears that patients with a CRP level ≥ 6 mg/l (high) were predominantly at an advanced T stage of cancer (62.2% vs 55.5%). But this difference was not significant P = 0.09as in the case of Ya-Jun Li et al, 2013 (P = 0.145). In oncology, tumor diameter is used to refer to the potentially palpable stage of cancer. However, there is no significant relationship between elevated CRP level and tumor diameter (P = 0.162). This result confirms that the level of CRP is not related to the stage T of the tumor. Similarly, Ya-Jun Li[10] corroborates this result by showing in his study that a diameter greater than or equal to 5 cm showed a non-significant association with the CRP level (P = 0.289). Once again, a non significant association was found between elevated CRP and the presence of lymph node (P = 0.111) and metastasis (p = 0,074). These results are close to the data provided by Cao[9] who showed a non significant association between lymphadenopathy (P = 0.297), metastasis (P = 0.183) and elevated CRP. Thus, our study shows that high CRP levels in patients with cancer and more at advanced stages reveal that the cancer is characterized by an inflammatory process. In contrast to the results found, several authors have shown the role of CRP in prognosis, taking into account advanced stage and survival. It appears that high circulating CRP levels correlated significantly with lymph node metastasis and survival in patients with oral SCC [11]. Ishizuka et al. [12] evaluated several potential clinical factors and biological markers in a large series of patients with locally advanced colorectal cancer. Multivariate analysis identified high CRP levels as an indicator or predictor of both nodal and distant metastasis in T3 colorectal cancer. Neuss et al. [13] demonstrated that the preoperative serum CRP level correlated significantly with the number of lymph node metastases found during radical lymph node dissection in stage III melanoma patients. Thus the role of CRP in cancer is still to be demonstrated because as shown in the review of Katriina Heikkila[14] nine large prospective studies identified in this review, four studies reported no association between circulating CRP and breast, prostate and colorectal cancers, but five studies provided some evidence that CRP could be related to colorectal and lung cancers. More over, several studies cumulate biases such as limitations in the selection of participants. In all, 41 studies did not contain an adequate description of how the participants had been selected that could influence the results found. Most prevalent studies have reported higher C reactive protein (CRP) concentrations in patients with cancer than in healthy controls and participants with some benign conditions, but this can be due to reverse causality, survival bias or confounding.However, some limitations of our study are that CRP was measured at one point in time. Therefore intra-individual variations were not considered. Furthermore, general diseases associated with possible higher inflammation markers like diabetes mellitus or Morbus Crohn were not taken into consideration due to lack of information.

Conclusion

At the end of our study whose objective was to evaluate the association between the rate of CRP and parameters of extension of cancers in the patients followed at the general hospital of Yaoundé, we found that there was a significant association between the high CRP level and the type of cancer. in other hand, the high rate of CRP was not significantly associated with the TNM parameters T (P=0.09), N (P=0,111) and M (P=0,074). hence circulating serum CRP level could not be a pronostic marker of cancer.

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