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Research Article

Phase I Diagnostic Study to Identify the Association Between Blood Eosinophilia and Ovarian Cancer Diagnosis

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Abstract

Objective: The purpose of this study was to identify the possible association between blood eosinophilia and the diagnosis of ovarian cancer.

Methods: A retrospective cross-sectional study of phase 1 development of the diagnostic test was carried out. Data was collected from the medical records of patients who consulted at the San Vicente Foundation Hospital in the emergency department or medical appointment with a diagnosis of ovarian tumor. The patients with confirmed diagnosis of ovarian cancer were the cases and those without this diagnosis were the controls.

Results: 199 histories were analyzed; of which 99 were from patients diagnosed with ovarian cancer. Out of the total of patients with ovarian cancer; 11.1% presented blood eosinophilia vs. 6% of the control (P = 0.197). Regarding the stage of the disease; III was the one that presented the greatest association with 20% of the cases.

Conclusions: We hypothesized that the frequency of eosinophilia would be twice as high in women with ovarian cancer compared to women without it, which was found in our results, 11% vs. 6%. Although this difference did not show statistical significance for several reasons; we consider the possibility of designing a subsequent phase II study in order to observe the probability that patients with a positive test (eosinophilia in blood) have the disease (ovarian cancer).

Keywords: Ovarian Cancer; Diagnosis; Blood Eosinophilia

Introduction

Ovarian cancer is the thirdmost common gynecologic malignant cancer and the second leading cause of death from gynecologic cancer in the United States [1]. For 2018, an incidence of 8.5 casesper 100 thousand inhabitants was estimated. Likewise, the projections of Globocan, Cancer Registry System of theWorld Health Organization reported that in Colombia the number of cases for the year 2018 was 8 per 100 thousand inhabitants and occupied the 7th place of a total of 54017 of all female cancers [2].

Ovarian cancer survival is related to stage at diagnosis, hence its 5-year survival is more than 95% when it is stage I [1], compared to 30% if detected in stage IV. However, it is one of the most difficult cancers to diagnose early, since the ovaries are not easily accessible, the symptoms that accompany it are vague and can be confused with those of other conditions that are not fatal [3], causing three out of four cases of ovarian cancers to be diagnosed in advanced stage [4].

Based on the assumption that cancer is a disease that benefits from early detection to achieve an increase in life expectancy, they

have studied a number of markers (Ca125, CEA and HE4) that could be used in those women with risk factors for ovarian cancer with the intention of allowing their early detection, but since they are very sensitive and not very specific, it has not been possible to impact the morbidity and mortality of these patients" [5,6].

Based on the knowledge that there is an increase in blood eosinophils in different types of cancers such as kidney, thyroid, liver, gallbladder, breast, pancreas and Hodgkin lymphoma [8] and that some of these organs originate from the intermediate mesoderm, as well as the ovary, it was hypothesized that Blood eosinophilia is more common in women diagnosed with ovarian cancer compared to women without a diagnosis. If this hypothesis is confirmed in this study, there would be justification to propose it as a predictor and in the future evaluate it as such, not only individually but included in prediction scales in conjunction with other factors.

Methodology

Study design

It is a retrospective cross-sectional phase 1 study of diagnostic test development, initial phase in the study of diagnostic tests in which they include confirmed cases and are compared with cases without the diagnosis. This phase of studies allows to identify promising evidence with which the most advanced evaluation process should be continued. Data were collected from the medical records of patients who consulted between January 2011 and January 2016 at the San Vicente Foundation Hospital in the emergency department or outpatient clinic.

The medical records were analyzed by 2 evaluators; we included those patients with diagnostic impression of both benign and malignant ovarian tumor with at least one blood cellogram at admission. We excluded those medical records of patients with atopy addent, who were currently undergoing parasitosis or diagnoses of Hodgkin lymphoma, colorectal cancer, breast and cervix. The population was divided into cases and controls, which had to meet the same criteria for inclusion and exclusion from the database. After reviewing the histories, women were considered as cases in which the report of ovarian cancer was confirmed with histopathology due to freezing or final pathology biopsy after surgery; and as a control, the medical history immediately following that history selected as a case and that the diagnosis of cancer had been ruled out was taken. If any discrepancies were found, both evaluators discussed the situation in question to reach an agreement.

Procedure

The blood counts reported in the clinical history were obtained only by assessing the information on eosinophils and the pathological history; the story was listed and the patient's name and ID record was concealed to ensure confidentiality. The value of eosinophils reported in absolute number was recorded in a table that also included the following variables: age, histological type and stage of ovarian cancer.

Eosinophilia was defined as an absolute eosinophil value greater than 500 µL. The sample size was not calculated but all the medical records recorded with this diagnosis were reviewed between the established dates, which in total were 1000. It was hypothesized that the frequency of eosinophilia would be twice as high in women with ovarian cancer compared to women without it.

According to resolution 008430 of 1993 of the Colombian Ministry of Health, this study classifies this study as a risk-free study. No data were taken to identify the women, codes were used for the assessment instruments and the database, and the list linking the code to the medical record number was kept in custody separately from the database. It was also evaluated and approved by the ethics committee of the San Vicente Foundation Hospital.

Statistical analysis

The distribution of quantitative variables was evaluated with the Kolomogorov-Smirnov test. The Mann Withney test was applied to assess differences in blood eosinophil values between women with and without ovarian cancer; the Chi2 test was applied to evaluate the association between histological type and eosinophilia in blood.

Results

From a total of 1000 medical records, after applying inclusion and exclusion criteria, 199 records were chosen; of which 99 were from patients diagnosed with ovarian cancer. Demographics and clinical findings are shown in table 1.

The numerical difference found in eosinophilia between the two groups, medians of 100 and zero (Table 1), was not statistically

Variables	Group I (Cancer = 99)	Group II (Control = 100)
Median Eosinophils (25th-75th Percentile)	100 (0-200)	0 (0-100)
Middle Ages/SD	50.42 (20.15)	45.43 (19.26)
Histological type		
Epithelial	27.3 % (27)	N/A
Germ cells	17.2 % (17)	N/A
Stromal cord	8.1 % (8)	N/A
Border line	14.1% (14)	N/A
Other (Undifferenti-ated)	3% (3)	N/A
No histological type	30.3% (30)	N/A
Stage		
SHE	6	N/A
IB	1	N/A
IC	2	N/A
IIA	3	N/A
IIB	2	N/A
IIIA	2	N/A
IIIB	8	N/A
IIIC	5	N/A
VAT	0	N/A
IVB	70	N/A
Unclassified		

Table 1: Demographics.

significant; El 11.1% of women with ovarian cancer had blood eosinophilia, compared to 6% of women without cancer, however, this difference was not statistically significant (P = 0.197) (Table 2).

	Cancer		Total
	No	Yes	
Eosinophilia	6(6%)	11(11.1%)	17(8.5%)
No eosinophilia	94(94%)	88(88.9%)	182(91.5%)
Total	100	99	199

Table 2: Blood eosinophilia in patients diagnosed with ovarian cancer and control cases.

Table 3 presents the value of blood eosinophilia in percentiles in patients diagnosed with ovarian cancer; which presented higher values in higher percentiles compared to controls.

Of the patients diagnosed with ovarian cancer, the histological germ cell subtype presented more eosinophilia with 17.6% followed by the epithelial subtype with 14.8% (Table 4).

In patients diagnosed with ovarian cancer and blood eosinophilia, stage III was the most associated with 20% of cases.

Eosinophils 5		Percentiles						
		10	25	50	75	90	95	
Cancer	NO	0	0	0	0	100	300	600
	YES	0	0	0	100	200	200	800

Table 3: Blood eosinophilia in patients diagnosed with ovarian cancer by percentiles

Histological type	Eosinophilia		Total
	Yes	No	
Epithelial	4(14.8%)	23(85.2%)	27
Germ cells	3(17.6%)	14(82.4%)	17
Estromal cord	1(12.5)	7(87.5%)	8
Border line	1(7.1%)	13(92.9%)	14
Other, includes in differenced	0(0%)	3(100%)	3
No histological type	2(6.7%)	28(93.7%)	30
Total	11	88	99

Table 4: Blood eosinophilia in patients with ovarian cancer according to histological subtype.

Stadium	Eosinophilia		Total
	Yes	No	
I	0(0%)	9(100%)	9
II	0(0%)	5(100%)	5
III	2(20%)	8(80%)	10
IV	0(0%)	5(100%)	5
Unclassified	9(12.9%)	61(87.1%)	70
Total	11	88	99

Table 5: Blood eosinophilia in patients with ovarian cancer by grouped stage.

Discussion

Ovarian cancer is a pathology characterized by in specific symptoms that makes it one of the most difficult to diagnose; According to the U.S. National Cancer Institute, three out of four cases of ovarian cancer are diagnosed at an advanced stage [4]. While an early diagnosis would impact patient survival, the various markers currently available that can guide diagnosis are not specific to it and are not available to all levels of care.

Eosinophils are granulocyte leukocytes found in the blood and in tissues such as the lung, breasts, gastrointestinal system, and reproductive system (ovary). These secrete a variety of proteins, cytokines and factors which can have antineoplastic or tumor progression-promoting effects. Among the proteins secreted after its activation, are the major basic protein and the cationic protein, which is polypeptides that have multiple functions but the most repressive is its cytotoxic effect on tumor cells [7]. Another of the secreted proteins is the neurotoxin, which has been observed in ovarian cancer and has been associated with poor outcomes in the patient [7].

Once eosinophils are in the tumor microenvironment, they secrete cytokines such as CCL5 that attract CD8 T cells to the tumor site and promote antitumor immunity. Likewise, CCL 3, 11, 17, 22, 23, CXCL 1, 5, 8, 9, 10 and 11 are added in order to recruit other leukocytes amplified and the initial response [10]; finally, it secretes factors such as growth transforming factor (TGF ALFA AND TGF BETA), vascular endothelial growth factor (VEGF) and vascular permeability factor which regulate epithelial proliferation, promote the formation of extracellular matrix, and the induction of angiogenesis, which have been implicated in prognostic and tumor progression [7].

With this background, it can be concluded that eosinophils have proteins, factors and cytokines that modulate the immune response associated with tumor progression, demonstrated in other types of cancer that share embryological and histological characteristics with ovarian cancer, which justifies the exploration of the hypothesis proposed for this research.

A systematic literature search was carried out in the PubMed, Embase and MedLine databases with the terms Mesh: "Ovarian Neoplasms", "Eosinophilia", "Eosinophil" and "blood"; the search was no restriction of year, no language limit and included cohort studies, case reports, letters to the editor, and literature reviews and found 10 articles in PubMed, of which 8 were excluded that were not related to ovarian cancer diagnosis.

2 articles are analyzed which are: a topic review where the role of eosinophilia in tumor immunity is discussed and mechanisms are proposed that explain its functional differences in the tumorogenesis of various types of cancer including ovarian cancer [7] and a second that reports the case of a 50-year-old woman who presented eosinophilia in blood during admission to the hospital in relation to abdominal symptoms. The main causes of eosinophilia, i.e. an allergic reaction, a parasitic infection and a haematological malignancy, were ruled out. Ultrasound of the total abdomen showed a mass in the lower abdomen that, due to the patient's history, was attributed to a uterine fibroid. Later, this tumor proved to be a mesenchymal neoplasm and surgery was performed to remove it. Histopathology confirmed a high-grade sarcoma that originated in the right ovary [9].

In Embase 17 articles were found: seven registered only in Embase, 9 articles in common with MedLine and only one of the latter, which was the case report already described. The others were excluded as they were not related to blood eosinophilia and ovarian cancer. Demonstrating in this way that although there are pathophysiological reasoning that relates the presence of eosinophilia with ovarian cancer, the available information is almost zero and no studies were found that would have ruled out the potential presence of this association.

A priori it had been hypothesized that the frequency of eosinophilia would be double in women with ovarian cancer compared to women without it, which was found in our results,

11% vs 6%, however, this difference did not reach statistical significance. Higher values were also found in the upper percentiles of women with cancer. Statistical significance may not have been achieved for several reasons, one of which was because the sample size was small. To achieve the required sample size, a multicenter study would be necessary.

Another reason was that 30% of the cases had no histological classification and 70% had no reported staging in the medical history, leading to an error detection of eosinophilia at the time of data analysis.

Being a potential economic diagnostic aid, easily accessible and interpreted at all levels of care, it could be easily applied in clinical practice. It is recognized that it is highly unlikely that a single marker can solve the problem of diagnosis in ovarian cancer, however, with the knowledge provided in the present research, the possibility of advancing in the phase of studies of diagnostic tests is open and if the proposed association is found, its usefulness could subsequently be tested in the context of the other existing tests, this could improve diagnostic performance by joining a score with other tests.

Conclusion

This study was established as phase I diagnostic tests and given the results obtained in it we consider open the possibility of designing a subsequent phase II study in order to observe the probability that patients with a positive test (eosinophilia in blood) have the disease (ovarian cancer).

Summary

Objective: The purpose of this study was to identify the possible association between blood eosinophilia and ovarian cancer diagnosis

Methods: A retrospective cross-sectional phase 1 study of diagnostic test development was conducted. Data were collected from the medical records of patients who consulted at the Hospital San Vicente Fundación in the emergency department or outpatient consultation with diagnosis of ovarian tumor. Patients with a confirmed diagnosis of ovarian cancer were the cases and those without this diagnosis were the controls.

Results: 199 stories were analyzed; of which 99 were from patients diagnosed with ovarian cancer. Of the total number of patients with ovarian cancer; 11.1% had blood eosinophilia vs 6% of the count (P = 0.197). In how much or at the stage of the disease; III was the one with the greatest association with 20% of the cases.

Conclusions: We hypothesized that the frequency of eosinophilia would be double in women with ovarian cancer compared to women without it, which was found in our results, 11% vs 6%. While this difference did not reach statistical significance for several reasons; We consider that the possibility of designing a subsequent phase II study in order to observe the probability that patients with a positive test (eosinophilia in blood) have the disease (ovarian cancer) remains open.

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