

The Relationship Between Serum Levels Of CA- 125 and Interleukin -6 with the Degree of Differentiation in Ovarian Neoplasms.

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ABSTRACT

Background: To study the serological correlation between serum levels of CA -125 and IL-6 with various histo morphological features of ovarian neoplasm.

Methods: Prospective study of two year duration from 2016 to 2018.Total of 40 women presented clinically with pelvic mass lesion were included. These patients undergoing concomitant serological analysis of CA -125 and IL-6. In each case, age, parity, marital life, radiological finding, histological type, degree of differentiation, extra ovarian tissues involvement was determined.

Result: Most of the ovarian neoplasm belongs to benign category 19/40 (47.5%) then malignant tumors 15/40 (37.5%). Surface epithelial tumours (80%) were common histopathological findings with raised CA-125 and Interleukin-6 levels. Most of the patient present with abdominal pain in their late reproductive age group (41-60 years). There is significant correlation (p-value=.000) in rise of levels of CA-125 and Interleukin-6 levels in patients with benign and malignant ovarian lesion. Levels of both the biomarkers are near normal levels in benign cases and levels were raised in malignant cases.

Conclusion: Amongst the ovarian neoplasm benign tumor were more common than malignant with predominance histological type is surface epithelial tumors. Serum levels of CA –125 and IL-6 were associated with histological grade in primary ovarian neoplasms, especially in high-grade malignant tumors, suggesting that high serological levels of these biomarkers are associated with lesions of more aggressive biological behavior.

Keywords: Ovarian Neoplasm, CA-125, Interleukin-6.

Introduction

Ovarian pathology is the widest and most complex problems in modern gynecology mainly through ovarian tumours. ^[1] Primary neoplasms of ovary comprise benign and malignant lesions, which may present superficial germinative epithelial -differentiation of the stromal sexual cord. It is the third most common site of primary malignancy in female genital tract after cervix and endometrium accounting for 30% of all cancers of female genital tract. ^[2]

Malignant ovarian tumors are responsible for approximately 6% of all cancers affecting women, and correspond to the seventh most frequent cause of death, for around 80% of the cases are diagnosed in advanced stages.^[3, 4]Ovarian cancer has an unknown natural evolution, starting often insidiously, without specific symptoms; the diagnosis is put during a routine exam. It is associated with an overall mortality of 75%, but can be cured in up to 90% of cases if diagnosed while still limited to the ovaries. Attempts to develop an effective screening strategy for ovarian cancer have utilized ultrasonography and serum tumor markers.

^[5]Despite the new techniques in imaging and genetics, the

diagnosis of ovarian tumours is primarily dependent upon histological examination.

Serological Tumor Markers For Ovarian Cancer

- CA125
- Carcinoembryonic antigen
- CA15-3
- TAG-72
- HMFG2 (Human milk fat globule)
- PLAP (Placental alkaline phosphatase)
- NB70/K
- Urinary gonadotropin core fragment peptide
- OVX1
- CA19-9
- LASA (Lipid-associated sialic acid)
- Tissue peptide antigen
- IL-6

Tumor Markers In Non Epithelial Ovarian Cancer

TUMOR MARKERS	TUMOR TYPE
fetoprotein (AFP)	Germ cell tumours
human -chorionic gonadotropin (beta-HCG) Placental alkaline phosphatase (PALP) Lactate dehydrogenase (LDH)	Dysgerminoma
Estradiol	Stromal tumours (including granulosa cell tumour)
Inhibin	Granulosa cell tumours

CA-125: The CA- 125 also known as MUC16 (sialomucin), is a glycoprotein synthesized by ovarian superficial cells. It is considered as the gold standard in the disease progression or even in the early diagnosis and clinical management of patients with ovarian tumors with epithelial differentiation. Normal blood levels are usually less than 35 U/ml. Its specificity seems to be low in benign tumours with or without epithelial differentiation and it's concentration is elevated in malignant tumors, principally in large lesions and/or advanced stages of the disease. More than 90% of women have high levels of antigen CA-125 when the cancer is advanced.

Interleukin -6: Interleukin-6 (IL-6) is a classic pro-inflammatory cytokine associated with a variety of pathological conditions, including cancer. Evidence supports the role of IL-6 in the pathophysiology of epithelial ovarian cancer (EOC) where the presence of an immunosuppressive network protecting tumor from immune system is also involved in EOC growth and progression. [6, 7, 8] IL-6 is produced by ovarian cancer cells and can be isolated from the ascitic fluid and serum of patients and it's higher levels have been found in patients with ovarian cancer, which have been shown to correlate with the extent of the disease and poor clinical outcome. [12,13,14, 15]

Materials and Methods

This prospective study of two year duration from 2016 to 2018 has been conducted in pathology department of Mahatma Gandhi Medical College and Maharaja Yeshwantrao Hospital, a tertiary care hospital of, Indore (M.P). Total of 40 women presented clinically with pelvic mass lesion probable of ovarian origin (Radio logically suggested) in the age group range from 11 years to 70 years were included. Patient with pelvic mass lesion of other than ovarian origin and already diagnosed cases of ovarian diseases were excluded. These patients undergoing concomitant serological analysis of CA -125 and IL-6. In

each case, age, parity, marital life, radiological finding, histological type, degree of differentiation, extra ovarian tissues involvement was determined.

Result

Most of the ovarian neoplasm belongs to benign category 19/40(47.5%) followed by malignant tumors 15/40 (37.5%). Borderline tumors comprising of 7.5%. Surface epithelial tumours (80%) were common histopathological findings with raised CA-125 and Interleukin-6 levels. Most of the patient present with abdominal pain in their late reproductive age group(41-60 years). There is significant correlation (p-value=.000) in rise of levels of CA-125 and Interleukin-6 levels in patients with benign and malignant ovarian lesion. Levels of both the biomarkers are near normal levels in benign cases and levels were raised in malignant cases.

Table 1: Out of 40 neoplastic lesions 32 are surface epithelial tumours (80%), 04 cases of germ cell tumours (10%) and 01 cases of sex cord stromal tumour (7.5 %) and 03 case in another category.

Most of the patients were of late reproductive age group i.e. 41 to 50 years of age (32.5%) followed by premenopausal age group (27.5%). Malignant tumours were more common in menopausal age group of 41 to 60 years of age while benign tumours were more common in reproductive age group of 31 to 50 years of age.

Table 2: Serum CA- 125 levels greater >35 U/ml found in 6 (31%) benign cases and 13(86%) malignant cases and CA- 125 levels >65 U/ml 3(15%) benign cases and 12(80%) malignant

Graph 1: showing significant correlation (p-value .000) of serum levels of CA- 125 and IL-6 in patient with benign lesion. Majority of patient with benign lesion have values of both serological markers near normal levels.

Graph 2: showing significant correlation (p- value .000) of serum levels of CA- 125 and IL-6 in patient with malignant lesion. Levels of both biomarkers are raised in malignancy but with higher levels of IL-6 than CA-125.

Table 3: Neoplastic lesions are more common in parous women having parity of three to four (45.0%), followed by (32.0%) of parity 1-2, followed by (17.5%) of parity >5 of tumors are found in grand multipara.

Discussion

At present there are advancements made in the fields of cancer screening and diagnosis but carcinoma of ovary remains the leading cause of mortality. In present study 40 cases were studied, includes 03 cases (7.5%) were

Table 1: Histological type of Neoplastic Lesions

Histological Type	Number of Cases	Percentage
Surface Epithelial Tumours	32	80%
Sex Cord Stromal Tumours	01	2.5%
Germ Cell Tumours	04	10%
Others	03	7.5%

Table 2: CA- 125, IL-6 Levels and Histo Pathological Findings

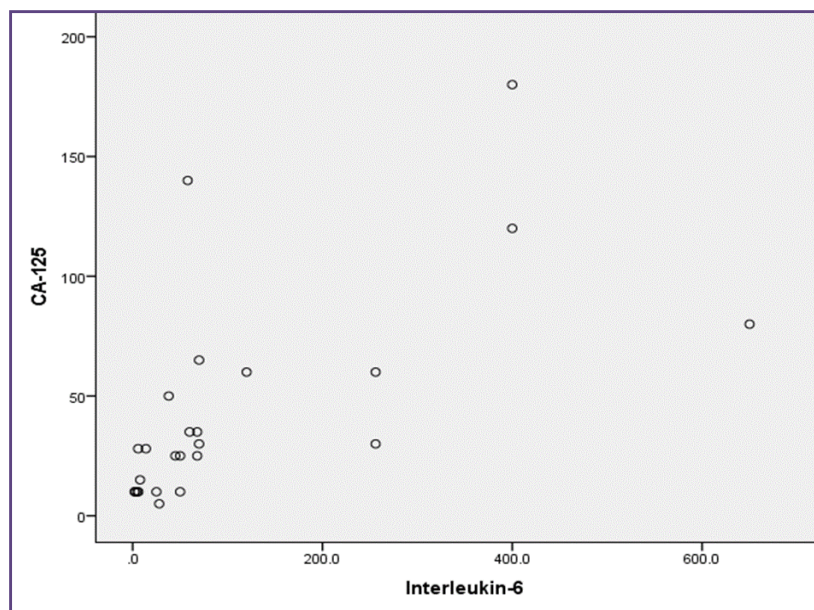
Histopathological Type	CA-125 (U/ml)		IL-6 (Pg /ml)	
	<35	>35	<(0-15)	>(0-15)
Benign	13	06	04	15
Borderline	00	03	00	03
Malignant	02	13	00	15
Others	03	00	03	00

Table 3: CA -125 and IL-6 Levels in Different Subtype

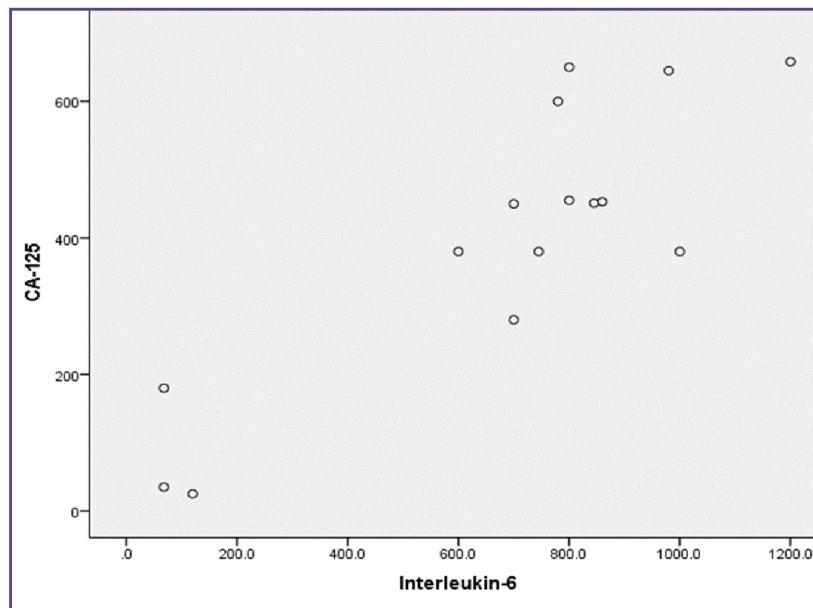
Histological Subtype	CA- 125 (U/MI)		IL-6(Pg/MI)	
	<35	>35	<(0-15)	>(0-15)
Surface Epithelial	12	20	00	32
Sex Cord Stromal Tumour	00	01	00	01
Germ Cell Tumour	04	00	04	00
Other	03	00	03	00

Table 4: Based On Degree of Differentiation of Malignant Lesion

Variables	Serum levels of CA -125		Serum levels of IL-6	
	<35 U/ml	>35 U/ml	< (5-15) pg/ml	>(5-15) pg/ml
Well differentiated	02	01	00	03
Moderately differentiated	00	02	00	02
Poorly differentiated	00	10	00	10



Graph 1: Correlation of CA- 125 and IL-6 Levels For Benign Lesion



Graph 2: Correlation of CA- 125 and IL-6 Levels For Malignant Lesion

non neoplastic lesion and 37 cases (92%) were found to be neoplastic. Of these neoplastic lesions 19 cases were benign 47.5%. Three cases 7.5% were borderline and 15 were malignant tumours 37.5% were recorded. Study done by Gupta N et al showed 72.9% benign, 4.1% borderline and 22.9% were malignant. Study done by Vidhi et al^[16] showed 66% benign and 34 % malignant tumours. Pilli et al^[17] had approximately similar results which showed that 75.2% ovarian tumours were benign, however this figure was only 59.2% in study carried in Pakistan by Ahmad *et al.*^[18]

Swami GC *et al* observed commonest histological pattern was epithelial tumor (61.6%). Kooning *et al* found that epithelial tumours represent 60% of all ovarian neoplasm and 85% of malignant ovarian neoplasm.^[19] Bushra *et al* also reported 96% epithelial tumours in her series.^[20] Vidhi et al^[16] found 73.58% epithelial tumours were diagnosed with 52 cases of malignant epithelial tumours accounting for 72.22% of all malignant neoplasms. R Jha & s Karki^[21] found surface epithelial tumours constituting 52% of all tumours followed by germ cell tumours (42%). In our study surface epithelial tumours constitute 80% of tumours followed by germ cell tumour (10%).

Borderline ovarian tumours are of low malignant potential having favourable prognosis and relatively early age at onset.^[22] They comprise 4%–14% of all epithelial ovarian neoplasms.^[23] We diagnosed total 03 borderline malignancies (7.5%), all 03 borderline cases in cases of borderline mucinous cystadenocarcinoma in 29 and 64 year

old females and one borderline serous cystadenocarcinoma in a 36 year female.

Of all the germ cell tumours, only mature teratoma is benign and is the most common lesion in this group.^[24] This is consistent with our findings.

Sex-cord stromal tumours constitute about 2.5% of ovarian neoplasms. These tumours bring extra interest because of their hormonal effects which are rare in other ovarian neoplasms. Granulosa cell tumour is the most common malignant sex-cord stromal tumour as well as the most common estrogen-producing ovarian tumour. Adult granulosa cell tumours are far more common than the juvenile type. They occur predominantly in peri- and postmenopausal women.^[25] This is comparable to our findings as we found 01 case of granulosa cell tumour.

Peak incidence of ovarian tumour is between 21-50 years.^[17] Benign ovarian tumours occur in all age group whereas malignant ovarian tumours are more common in elderly,^[26] Majority of benign serous tumours occur in 4th–6th decade although they may occur in patients younger than 20 or older than 80 years. Serous carcinomas are extremely rare in first two decades of life, average patient age for serous carcinomas is 56 years. Mucinous cystadenoma may occur at any age but are most often diagnosed in 4th–6th decade. Mucinous cancers have mean age of 53-54 yrs. We also found nearly similar results.

Maximum of the patient with malignancy were over 45 years 32.5% which is comparable to study done by Chakrabortti and Lee.^[27]

Nulliparity is considered to be a risk factor for the development of ovarian carcinoma. Most of the western studies have shown that nulliparous women have high incidence of ovarian cancers. According to these studies multiparity was associated with a significant reduction in risk of ovarian cancer and the high risk of ovarian cancer is inversely related to the number of full-term pregnancies and each additional sibling as associated with a risk reduction.^[28-31] However, the majority of our patients of ovarian tumours were having children (87%) and a lesser number of patients turned out to be nulliparous (13%). Of 31 patients suffering from ovarian carcinoma 19(61%) had a parity of 1-4, 07 patients (23%) had a parity of 5 or more and 05(16%) were nullipara.

Ovarian tumours in the pediatric age group are not infrequent, Oumachigui *et al*, 1991. found the incidence to be six per cent of all ovarian tumours. Sawai and Sirsat recorded the incidence as 11.2%⁶ (Sawai MM *et al*, 1973). present study show 5.4% in paediatric age group.

We found abdominal pain in 45% of cases as most common presenting complaint followed by abdominal distension in 32.5% and backache in 12.5%. Gonsai *et al* found these findings in 52%, and 16% cases respectively.

Kolwijck *et al*. describe that the pre-operative serum CA 125 levels are significantly higher in advanced lesions and in serous tumors.^[32]

Osman *et al*. report that postoperative serum CA 125 levels are associated with stage, histologic grade and survival in cases of ovarian carcinoma.^[33]

Berek *et al*.³⁴ recently published data from 36 patients with epithelial ovarian cancer and concluded that IL-6 may be a useful tumor marker in this disease, because it correlated with tumor burden, clinical disease status, and survival time.

Conclusion

Amongst the ovarian neoplasm benign tumor were more common than malignant with predominance histological type is surface epithelial tumors. Serum levels of CA-125 and IL-6 were associated with histological grade in primary ovarian neoplasms, especially in high-grade malignant tumors, suggesting that high serological levels of these biomarkers are associated with lesions of more aggressive biological behavior. It helps in effective therapeutic management of ovarian malignant tumours. An accurate diagnosis of ovarian malignancy by serological evaluation CA-125 and IL-6 and by histopathological diagnosis will help in rendering prompt and appropriate treatment to the patient.

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