Journal of Cancer Diagnosis

Short Communication Open Access

# Salivary Type Hyperamylasemia as a Sign of the Presence of Ovarian Cancer

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**Abbreviations:** CA125: Carbohydrate Antigen 125; HE 4: Human Epididymis Secretory Protein E4; CEA: Carcinoembryonic Antigen; CA 19.9: Carbohydrate Antigen 19.9; FIGO: International Federation of Gynecology and Obstetrics; OC: Ovarian Cancer

## Introduction

Lifetime risk of developing Ovarian Cancer (OC) in women is 13% (1 in 75). Unfortunately, only a minority of cases (15%) are diagnosed in stage 1, with a 5-year survival rate of 92%. Conversely, at a late stage, when mostly patients are diagnosed, it is only 29% [1]. Serum tumor markers are largely used in gynecological malignancies. Among them, Carbohydrate Antigen 125 (CA 125) certainly is the most used in OC. Despite its lack of specificity, as it can be found elevated in different malignant and non-malignant conditions, such as the presence of pleural or peritoneal effusion, it has been widely used to help predicting the nature of a pelvic mass as well as during cancer treatment and its follow-up. Differently, amylase, an enzyme that catalyzes the hydrolysis of starch, is not currently used as a marker in clinical practice. Nevertheless, high salivary-type amylase levels have been found in some cancers, such as lung adenocarcinomas and ovarian cancer, as well as in benign conditions, as its genes are expressed in many organs, including lung, trachea, ovary, Fallopian tubes, and uterine cervix [2-4]. Amylase is encoded by two different loci: AMY1 and AMY2.

AMY1 is responsible for extra-pancreatic and extra-salivary production of amylases 2 while AMY2 is implied in pancreatic production of amylases. The role of amylase genes in tumorigenesis isn't clear, but AMY2A has been reported to be a potential tumor-suppressor gene in gastric cancer [5]. Here we report a case of hyperamylasemia in a patient with ovarian carcinoma.

## About the Study

A 47-year-old Caucasian woman, with a history of early onset menopause at the age of 36 (since then taking hormone replacement therapy) and no history of familial breast and ovarian cancer was admitted to our institution on January 2019. She referred abdominal swelling and diffused soreness that started 6 months earlier. Her last medical examinations, including PAP test, abdominal and vaginal ultrasonography, were all normal in 2018. After various clinical investigations, including vaginal ultrasonography and Computed Tomography (CT) scan, she was diagnosed with peritoneal carcinomatosis of suspected ovarian origin. Blood tests showed high levels of CA 125 and CA 15.3 (717.8 U/ml and 50.9 U/ml, respectively), whereas CEA and CA 19.9 were normal. Interestingly, total amylase levels were unexpectedly high, reaching a value of 413 U/L (upper normal limit 100 U/L). Therefore, we measured out pancreatic-type amylase, which resulted being within the normal range (43 U/L), suggesting the increase of salivary-type amylase. Lipase levels were normal. Laparoscopy and biopsy were then performed and documented high grade serous ovarian cancer (FIGO stage IIIC), not surgically cytoreductable (Fagotti score=8). Therefore, neoadjuvant chemotherapy with Carboplatin plus Paclitaxel was administered, obtaining a good response either on imaging or laboratory (CA 125: 76 U/ml on March 18, 2019). On April 29, 2019, patient was finally able to undergo optimal cytoreductive surgery (no macroscopic residual). After surgery, blood test documented a normalization of amylase levels.

## Discussion

Elevated amylase serum levels are typically associated with pancreatitis, but can occur in several kinds of diseases and even in psycho-social stress conditions and stress-related anxiety [6]. Their association with cancer was reported for the first time in 1951, while the specific association with OC dates back to 1976 [7,8]. The underlying cause of the increased serum amylase in our patient is unknown, as she didn't have pancreatic abnormalities or other conditions that could explain this finding. Their production could hypothetically be the result of AMY1 expression due to the genetic changes that occur during neoplastic transformation, giving to OC cells some features that resemble other cell lines that normally produce this enzyme. Amylase, for its part, could contribute modifying tumor microenvironment, favoring tumor invasiveness. Interestingly, a Homozygous Deletion (HD) of AMY2A gene seems to be involved in human carcinogenesis, as reduced copy number of this gene has been frequently found. In particular, HDs at 1p21.1, the region harboring AMY2A, were identified in 5 out of 27 (18.5%) patient with gastric cancer, strongly suggesting a role as a tumor-suppressor gene 5. This was also supported by a study published in 2015, suggesting that altered AMY2B and AMY2A copy numbers could play a role in the tumorigenesis of lung squamous-cell carcinoma via the starch and sucrose metabolism pathway [9]. Kawakita , et al. compared women with OC with women affected by benign ovarian tumors and documented a significantly higher incidence of hyperamylasemia in the first group, with a sensitivity of 21.4% and a specificity of 93.5% [10]. Interestingly, a report of an OC case with elevated serum amylase, published in 2014, documented that the elevation of this enzyme was noted two years prior to the diagnosis, highlighting a possible role on early diagnosis, maybe in conjunction with other commonly used tumor markers, such as CA 125 [11]. Furthermore, similarly to the case report here described, the patient had an excellent response to chemotherapy. This suggests the need of a further evaluation of responsiveness to chemotherapy in the subgroup of OCs with elevated blood amylase level. The main limitation in this case report was the lack of a confirmed source of amylase production, as its expression by the tumor wasn't confirmed by an immune histochemical staining.

Further studies investigating the usefulness of amylase in conjunction with other tumor markers, such as CA 125 and HE-4, and its possible role as a prognosis marker are needed, as well as defining a proper cut-off for this marker. Meanwhile, physician should be aware about the possibility of the presence of an occult tumor, in particular OC, in patients showing high levels of serum amylase without any other sign, after ruling out the most

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**Received:** November 03, 2020; **Accepted:** November 17, 2020; **Published:** November 24, 2020

**Citation:** di Federico A, Filippini DM, Rubino D, Mandrioli A, Zamagni C (2021) Salivary-Type Hyperamylasemia as a Sign of the Presence of Ovarian Cancer. J cancer diagn 5: 123.

common causes.

## Conclusion

Physician should be aware about the possibility of the presence of an occult tumor, in particular OC, in patient showing high levels of serum amylase in the absence of other known hyperamylasemia causes. Further studies investigating the usefulness of amylase in conjunction with other tumor markers, such as CA 125 and HE-4, are needed.

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