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Review article

Paraneoplastic antigens as biomarkers for early diagnosis of ovarian cancer

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ABSTRACT

Paraneoplastic syndromes are a group of rare disorders that can be triggered by an abnormal immune response to proteins from tumors of the lung, ovary, lymphatics, or breast. Paraneoplastic clinical syndromes affect < 1% of patients with cancer; however, the frequency of subclinical levels of paraneoplastic autoantibodies in asymptomatic patients with cancer is unknown. Numerous studies have reported that ovarian cancer patients show signs of paraneoplastic neurological syndromes (PNSs) before or after their cancers are diagnosed. PNSs arise from a tumor-elicited immune response against onconeural antigens that are shared by tissues of nervous system, muscle, and tumor cells. Studies on the serum IgGs obtained from ovarian cancer patients have indicated the presence of onconeural antibodies in the absence of any PNS symptoms. The occurrence of PNSs is low in ovarian cancer patients and it can be accompanied by onconeural antibodies. The diagnosis of PNSs is accompanied by a suspicion of a malignant tumor such that neurologists typically refer such patients for a tumor diagnostic workup. There will be tremendous utility if subclinical levels (without paraneoplastic neurological symptoms or myositis) of these autoantibodies to paraneoplastic antigens can be exploited to screen asymptomatic high-risk patients for ovarian cancer, and used as biomarkers in immunoassays for the early detection or recurrence of ovarian cancer. Ovarian cancer overall survival is likely to be improved with early detection. Therefore, a panel of onconeural antigens that can detect paraneoplastic autoantibodies in patient sera should provide diagnostic utility for an earlier therapeutic intervention. Here we review the usefulness of PNS and other paraneoplastic syndromes and their association with paraneoplastic antigens to exploit these autoantibody biomarkers to form diagnostic multi-analyte panels for early detection of ovarian cancer.

1. Introduction

1.1. Historical background of the discovery of paraneoplastic syndromes

Paraneoplastic syndromes are rare heterogeneous disorders that are characterized by the presence of endocrinological, neurological or dermatological syndromes. These disorders arise from the secretion of hormones from the tumor, or can be an autoimmune response elicited by tumor cells against onconeural antigens common to both the nervous system and to an underlying tumor (Pelosof and Gerber, 2010). The occurrence of paraneoplastic symptoms leads physicians to explore for the presence of cancer as the symptoms can appear prior to clinical manifestation of cancer. In 1825, Armand Trousseau first described the existence of a paraneoplastic syndrome called “Trousseau's Syndrome” in a gastric cancer patient who was also diagnosed with venous thrombosis. It has been reported that pancreatic, lung, and gastric cancer are associated with this syndrome, which typically appears months to years before the clinical diagnosis of a tumor (Callander and Rapaport, 1993). Hermann Oppenheim in 1888 was the first to suggest that neurological symptoms in patients with cancer could be directly connected to the underlying tumor (Schulz and Pruss, 2015). In 1912, Harvey Williams Cushing reported an endocrinological syndrome caused by a malfunction of the pituitary gland which he termed “Cushing's syndrome” (Cushing, 1994). Li et al. reported the incidence of Cushing's syndrome due to the presence of a multiple endocrine neoplasia type-1 (MEN-1) associated thymic neuroendocrine tumor (Th-NET). In 1948, Derek Ernest Denny-Brown documented a case study of two patients who had primary simple degeneration of the dorsal root ganglion cells associated with a primary degeneration of the muscles called “polymyositis”. Both of the patients who presented symptoms of severe neuropathy and ataxia had previously been diagnosed with bronchogenic pulmonary carcinoma (Denny-Brown, 1948). In 1929, Casper and in 1951, Brain et al. reported case studies that demonstrated the association of subacute cortical cerebellar

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degeneration with cancer (Brain et al., 1951). In 1968, Corsellis et al. defined “paraneoplastic limbic encephalitis” (PLE) in a study of three patients in which one patient developed memory loss that increased over a period of months and the two other patients had bronchial carcinoma associated with dementia (Corsellis et al., 1968). In 1985, Graus et al. reported the presence of neuronal antinuclear autoantibodies in four patients with subacute sensory neuropathy and small cell carcinoma of the lung (Graus et al., 1985).

The discoveries of various endocrinological, neurological and dermatological syndromes that are caused by the underlying cancer, have led neurologists to coin the term “paraneoplastic syndromes”. Paraneoplastic neurological disorders occur in the central or peripheral nervous system and can result in muscle weakness and brain degeneration, leading to immobility and death. Clinical symptoms of paraneoplastic syndromes may include loss of muscle tone, slurred speech, memory loss, vision problems, dementia, ataxia, seizures, and sensory loss in the limbs. An international panel of PNS experts has recommended consensus criteria for diagnosis of PNS (Graus et al., 2004). Paraneoplastic syndromes, if diagnosed correctly by the physician, may help to diagnose an underlying cancer before its clinical symptoms. The epidemiology of the paraneoplastic neurological disorders varies from cancer to cancer. Studies have shown that approximately 0.5–1% of all cancer patients have a clinically diagnosed PNS (Rees, 2004). This review will focus on the incidence and association of various PNSs with ovarian cancer, the pathogenesis of PNS in ovarian cancer, and the potential for onconeural antibodies to be useful tools to detect ovarian cancer at an early and potentially curable stage.

2. Incidence of paraneoplastic syndrome in ovarian cancer

Symptomatic paraneoplastic disorders are rare in patients who have gynecological cancers, and the incidence of occurrence is approximately 1 per 1000 new cases (Rees, 2004). PNSs that are most commonly associated with ovarian cancer include paraneoplastic cerebellar degeneration, dermatomyositis and polymyositis (Zahr and Baer, 2011). Women presenting with these syndromes are referred for evaluation of ovarian cancer. It has been reported that 0.1% of patients with subacute cerebellar degeneration develop ovarian carcinoma (Abrey and Dalmau, 1999). Symptoms of paraneoplastic cerebellar degeneration include ataxia, lack of balance, speech dysfunction, and nystagmus. Polymyositis is an inflammatory myopathy resulting in muscle weakness, and is associated with dermatomyositis, in which inflammation manifests in skin rashes and can co-occur with muscle weakness. Patients with either syndrome are at higher risk for malignancy.

In 1965, a survey of incidence of carcinomatous neuromyopathy in cancer patients was reported by Croft and Wilkinson. In the survey, out of 55 patients with ovarian cancer, only 9 patients were reported to have carcinomatous neuromyopathy (Croft and Wilkinson, 1965). Dalmau et al. assessed 121 neurologic consultation reports that were obtained from 83 ovarian carcinoma patients who were seen between 1993 and 1996. In that study, 38 patients were reported to develop peripheral neuropathy after the completion of chemotherapy. PNSs were observed in 4 patients; 1 patient was diagnosed with dermatomyositis and 3 patients were diagnosed with subacute cerebellar degeneration (Abrey and Dalmau, 1999). In 2010, a population based European study was reported by Giometto et al. that represented PNS association of 979 patients (968 patients had definite PNS and 11 patients had possible PNS; 899 patients had data available) recruited between 2000 and 2008 by applying the diagnostic criteria provided by Graus et al. (Graus et al., 2004). Analyses of the data that was collected from PNS Euro network database showed that 94 out of these 899 (10.5%) had ovarian cancer patients associated with a PNS (Giometto et al., 2010). In 2001, Hill et al. reported a pooled analyses of the incidence of dermatomyositis and polymyositis in cancer patients using the national data obtained from Swedish National Board of Health that spanned between 1964 and 1983, Finnish National Board of Health from 1969 to 1985, and Danish Hospital Discharge Registry from 1977 to 1989. Their study population was comprised of 618 patients with dermatomyositis, out of which 198 had cancer and 115 out of 198 patients were diagnosed with dermatomyositis prior to the cancer development. Their study showed that the standardized incidence ratio (SIR) was 10.5, at 95% confidence level (CI (6.1–18.1)) for women who developed dermatomyositis prior to diagnosis of ovarian cancer, indicating a strong association of dermatomyositis prior to symptoms of ovarian cancer (Hill et al., 2001).

3. Presentation of paraneoplastic syndromes with ovarian cancer

Numerous studies detailed the findings of PNSs with ovarian cancer. In 2000, Forgy et al. documented a case report of a patient who was diagnosed with two PNSs, nephrotic syndrome and paraneoplastic cerebellar degeneration prior to the diagnosis of ovarian cancer. CT scan and ultrasound were performed later for the evaluation of malignancy that revealed the presence of 5 cm ovarian mass and multiple paraaortic lymph nodes. Tirmzay et al. reported a case history of a 75-year old woman with stage III serous ovarian carcinoma who developed peripheral mixed sensory and motor neuropathy after surgery and chemotherapy. Eleven months after her last chemotherapy, the PNSs persisted. She developed ataxia and pseudoathetosis beside other prevailing PNSs (Tirmazy et al., 2014). Li et al. presented a case study of a 37-year old woman who developed paraneoplastic cerebellar degeneration and limbic encephalitis following Hepatitis-B vaccination. The symptoms included ataxia, slurred speech, involuntary movements of arms, depression, aggressive behavior, dysphagia and hypomnesia. The occurrence of paraneoplastic Yo antibodies were confirmed in both CSF and serum with a concurrent serum CA125 highly elevated at 2752 U/ml. The patient was diagnosed with high-grade, stage IIIc ovarian serous papillary cystadenocarcinoma. After the completion of chemotherapy and cyto-reductive surgery no ovarian cancer recurrence was observed after 38 months from diagnosis (Li et al., 2015). Hong et al. reported a case study of a 48-year old patient who had multiple erythematous skin rashes on her face, forehead, knuckles and anterior chest area. Bilateral knuckles were found to have Gottron's papules with impairment of her speech and hearing as well as weakness in muscular strength around her shoulders and leg with concurrent increased levels of aspartate aminotransferase (148 IU/l), alanine aminotransferase (130 IU/l), total creatine kinase (1190 U/l) and CA125 (543 IU/ml). The patient was diagnosed with dermatomyositis. Based on transvaginal ultrasound and MRI, the patient underwent optimal debulking, total hysterectomy and bilateral salpingo-oophorectomy due to the presence of stage IIIc high grade ovarian serous carcinoma. After the surgery, all PNSs disappeared (Hong et al., 2015). Scholz et al. reported a case study of a 45-year old woman who had problem walking because of the development of generalized shivers. She was diagnosed with opsoclonus, associated with conjugated eyes that showed movement arrhythmically in all directions. Myoclonic speech associated with dysarthria was noted. PNSs, such as truncal ataxia and limb ataxia were also observed with elevated levels of carcinoembryonic antigen (5 ng/ml) and CA125 (2161 units/ml). The presence of tumors on both her right and left ovaries was confirmed after an abdominal CT and laparotomy with a diagnosis of stage IIIc ovarian carcinoma (Scholz et al., n.d.). Appearance of Cushing syndrome in a 61-year old woman prior to the diagnosis of ovarian cancer has been reported. Two-site immunoradiometric assay (IRMA) was performed to measure the levels of Adreno corticotropic hormone (ACTH) and its precursors with blood serum and urine analysis revealing the elevated CA125 level (214.6 U/ml) and cortisol level (496 nmol/24 h). Pelvic ultrasound followed by laparotomy confirmed the presence of multicystic right ovarian mass confirmed at surgical resection as ovarian carcinoma. Hydrocortisone treatment followed by chemotherapy resulted in a long disease free interval as indicated by her post 4 years of follow-up (Al Ojaimi, 2014).