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Case Report

Microscopic Dysgerminoma Associated With *Anti-Ma2* Paraneoplastic Encephalitis in a Patient With Gonadal Dysgenesis

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Summary: We present a 27-yr-old female with gonadal dysgenesis (46, XY), who presented to our hospital with poor consciousness, aphasia, restlessness, and visual hallucination. Physical examination revealed normal breast development and normal external female genetalia. Computed tomography scan of the head and neck revealed the presence of brain edema, hydrocephalous, and a localized hypodense lesion in the hypothalamus. Her serum was positive for the *anti-Ma2*, which is associated with paraneoplastic encephalitis syndrome. Computed tomography of the abdomen revealed the presence of a 7.5 × 5.3 × 3.0 cm solid pelvic mass. Interestingly, a single microscopic focus of dysgerminoma was identified in a background of stromal fibrosis and focal dystrophic calcifications. No ovarian stroma or testicular tissue was identified. To our knowledge, this is the first case of gonadal dysgenesis presenting with *anti-Ma2* paraneoplastic encephalitis with dysgerminoma. A discussion about paraneoplastic encephalitis with a microscopic dysgerminoma associated with *anti-Ma2* antibody is presented. **Key Words:** Dysgerminoma—*Anti-Ma2*—Paraneoplastic syndrome.

Gonadal dysgenesis encompasses a heterogeneous group of different chromosomal, gonadal, and phenotypic abnormalities. This includes 45, X Turner syndrome and its variants, mixed gonadal dysgenesis, and 46, XX and 46, XY pure gonadal dysgenesis. The latter includes a complete and a partial form, where individuals with 46, XY gonadal dysgenesis have abnormal testicular determination (1). Histologic examination is vital to determine the exact form of gonadal dysgenesis. In the complete form of 46, XY pure gonadal dysgenesis, patients present with 46, XY karyotype, bilateral streak gonads, absent Wolffian structures (seminal vesicles, vas deferens, and epididymis), and well-developed Mullerian structures (uterus, fallopian tubes, and upper third of the vagina) (2). Individuals with mixed gonadal dysgenesis have a streak gonad on 1 side and a normal-appearing or dysgenetic or abnormally formed gonad on the opposite side. The development of Mullerian and Wolffian structures usually depends on the histology of the ipsilateral gonad. In contrast, individuals with partial gonadal dysgenesis have bilateral dysgenetic testes that include poorly formed seminiferous tubules and ovarian-like stroma. In both mixed and partial gonadal dysgenesis, the development of the external genitalia or phenotype may be ambiguous. It has been postulated that the presence of the Y chromosome in these 46, XY patients increases the risk of developing gonadal tumors such as gonadoblastoma or dysgerminoma by 10% to 30% (3–7).

Neurological paraneoplastic syndromes incorporate a broad range of disorders thought to result from

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"collateral damage" to the nervous system (8–10). It was hypothesized that this phenomenon is most likely the result of an exaggerated immune response to some neoplastic antigens (11). This immune response may be explained by cross-reactivity to antigens that are incidentally expressed by healthy neural tissue. These primary neoplasms are typically malignant and are often small and difficult to identify, possibly because it is sometimes markedly contained by an aggressive immune response. Notably, the paraneoplastic syndrome may appear months or even years before the underlying malignancy is identified (12).

Paraneoplastic neurological syndromes include paraneoplastic limbic encephalitis, which is often associated with small cell lung carcinoma and testicular germ cell tumors (13). The clinical syndrome associated with *anti-Ma2* antibodies was recognized in 1999 by Voltz et al. (14). The *Ma2* gene encoding the target antigen is a member of the paraneoplastic "Ma" family of onconeuronal proteins, and is expressed by both testicular cancer cells and normal brain tissue, particularly in the limbic and the brainstem regions. *Anti-Ma2*-associated encephalitis (*anti-Ma2*AE) has been identified in association with many different neoplasms, the most frequent of which is germ cell tumor of the testis. *Anti-Ma2*AE is difficult to diagnose, and a testicular malignancy is often overlooked. In contrast to other paraneoplastic syndromes that usually evolve over fewer than 8 wk, patients with *anti-Ma2*AE have a longer median time in the range of 6 to 12 mo from the onset of symptoms (range 5 d–16 mo). The protracted time course and confusing constellation of findings frequently lead to more diagnostic delays.

Routine diagnostic tests will often reveal normal results or nonspecific abnormal results. In 50% of cases, a lumber puncture will reveal pleocytosis, and in 63% of cases, there will be nonspecific markers of inflammation or altered protein synthesis in the form of elevated protein or oligoclonal bands. In 74% of cases, brain magnetic resonance imaging scans are abnormal, and often demonstrate T2 fluid-attenuated inversion recovery hyperintensities in the limbic and the brainstem regions that will occasionally be enhancing. The standard criterion for diagnosis is the identification of *anti-Ma2* antibodies in either the serum or the cerebrospinal fluid in the appropriate clinical context.

To the best of our knowledge and after reviewing the English language literature, we present the first case of pure gonadal dysgenesis with a tiny focus of dysgerminoma presenting clinically with *anti-Ma2* paraneoplastic encephalitis.

CASE PRESENTATION

A 27-yr-old married Saudi lady was known to have testicular feminization syndrome diagnosed 10 yr ago. She presented to our emergency room with agitation, hallucinations, and confusion. We discovered that she was admitted before to another medical facility for 2 mo with similar complaints and was diagnosed with hypothalamic encephalitis and hence managed accordingly.

The basic hematological and biochemical parameters were evaluated. Cerebrospinal fluid analysis was negative for malignant cells, whereas computed tomography scan of the brain showed a symmetrical periventricular low attenuation around the third ventricle (Fig. 1). Her serum *anti-Ma2* was sent to a referral laboratory outside the Kingdom and returned as positive. Computed tomography scan of the abdomen and pelvis revealed the presence of a 7.5×5.3 cm left solid adnexal mass along with multiple enlarged para-aortic lymph nodes (Fig. 2 top). Ultrasound examination of the pelvis showed a uterus of an average size (6.6×2.5 cm). No obvious adnexal structures were identified.

A human immunodeficiency virus test was nonreactive and the other tumor markers levels were as follows: carbohydrate antigen (CA) 125 of 63 IU/mL (0–42.4 IU/mL), CA 19.9 of 2 IU/mL (0–37 IU/mL), CA 15.3 of 21 IU/mL (0–27 IU/mL), α-fetoprotein of 2.81 ng/mL (1.09–8.04 ng/mL), β-HCG of 1.2 IU, estradiol (E2) < 37 pmol/L, follicle stimulating hormone = 0.3mIU/ml, luteinizing hormone < 0.07 mIU/mL, testosterone < 0.28 nmol/L, and thyroid stimulating hormone 0.01 mIU/L (0.35–4.94 mIU/L).

Initially, surgical removal of the tumor was not advised because of her unstable hemodynamic condition and altered consciousness level. She was then transferred to the intensive care unit where she was managed as a case of panhypopituitarism. She was given hormonal supplements and desmopressin, hydrocortisone, and antibiotics. After she improved and became stable, she underwent laparatomy. She had left gonadectomy, excision of the pelvic mass, omentectomy, pelvic lymph nodes dissection, and para-aortic lymph node sampling. She had a small, not well-developed uterus communicating with the vagina. No right gonadal tissue was seen and no intraperitoneal nodules were noted. The diagnosis

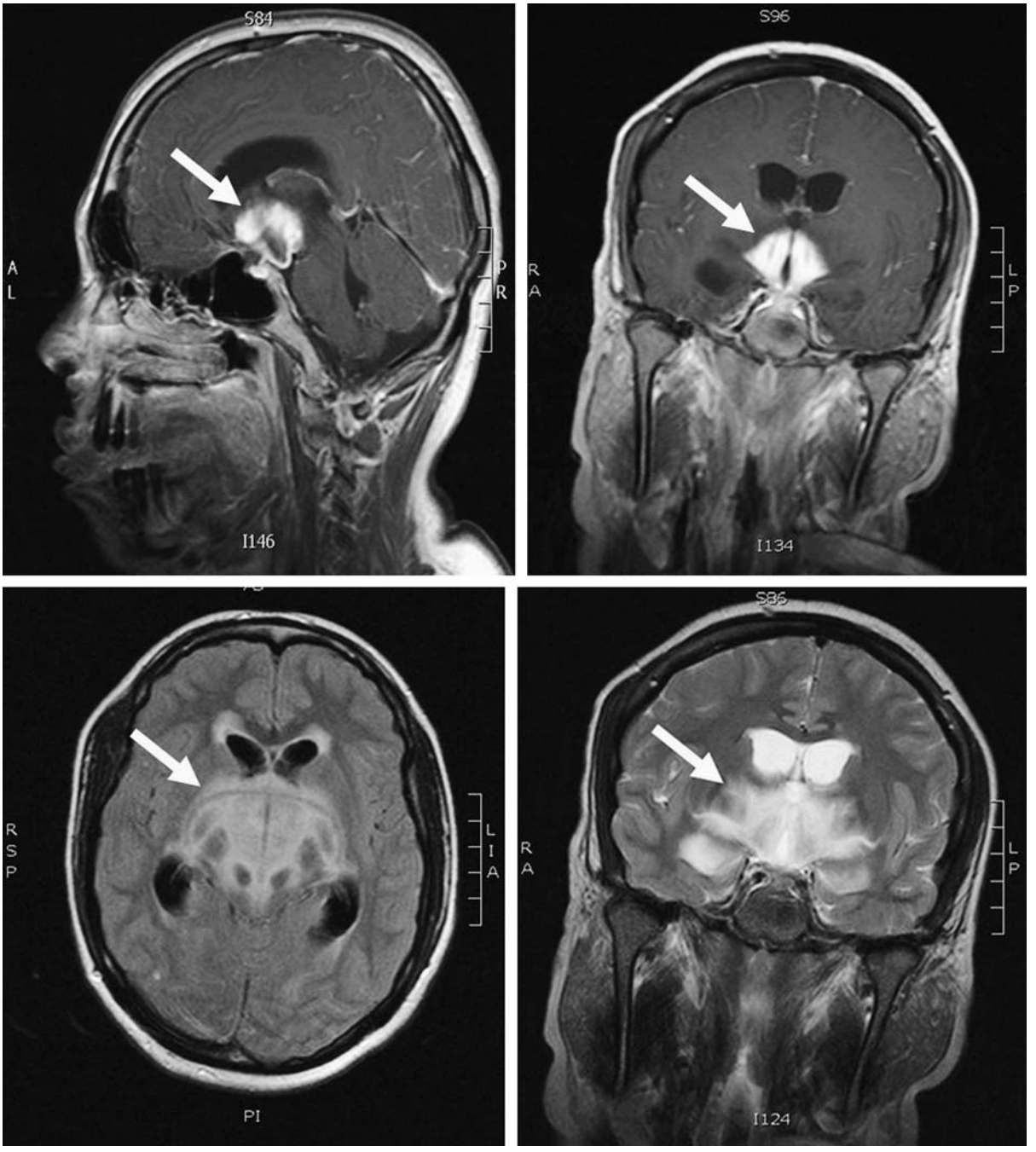

FIG. 1. The top arrows show intense symmetric enhancement in the hypothalamus in the sagittal and coronal planes. The bottom left arrow points at extensive edema on flair axial image while the bottom right one shows extensive surrounding edema in the coronal plane.

of *anti-Ma2*-associated paraneoplastic encephalitis syndrome was finally made. Postoperatively, she improved slightly, but continued to suffer from electrolyte imbalance and was discharged on medical treatment.

The mass had a smooth shiny external surface and measured $7.5 \times 5.3 \times 3.0$ cm. The cut surface of the mass was solid, fleshy, lobulated and gray-yellow, and homogenous (Fig. 2 bottom). There were no areas of hemorrhage, necrosis, or cyst formation. A single fallopian tube was identified measuring 4 cm in length, and no recognizable ovarian tissue could be identified on gross examination of the specimen.

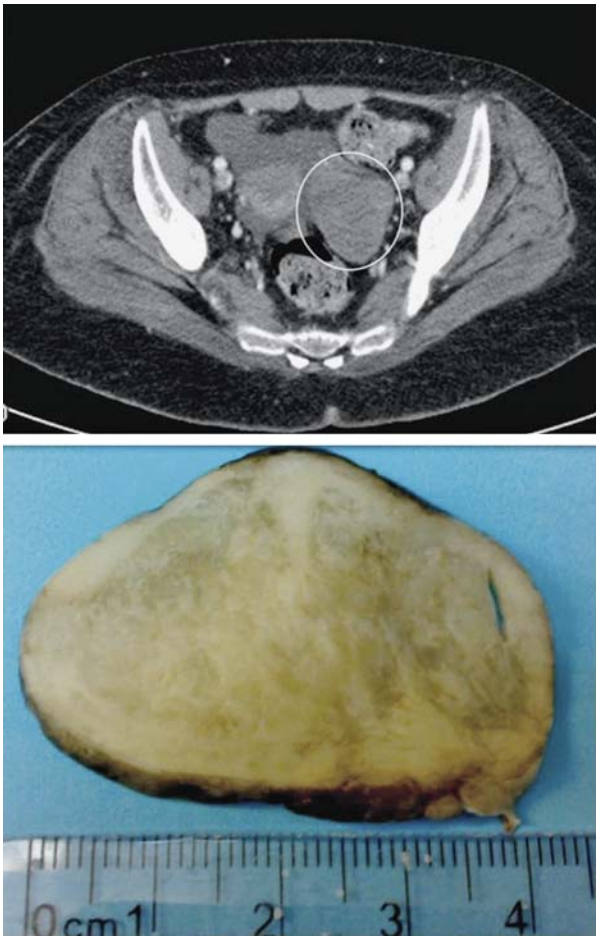

FIG. 2. Computed tomography scan of the pelvis showing a well-circumscribed left adnexal mass (top). The cut section is homogenous white-yellow in color and firm in consistency (bottom).

Approximately >90% of this mass was sampled for routine histologic examination (to be exact, 34 paraffin blocks were submitted). Histologic examination of the mass revealed extensive sclerosis and hyalinization with foci of dystrophic-type calcifications. The calcification were purple in color and were irregular in shape and seen embedded in the hyalinized stroma. The fallopian tube sections revealed normal tubal mucosa with unremarkable Mullerian-type epithelium and underlying muscle coat with no evidence of tumor or any other histologic abnormalities. Despite extensive sampling, no definite ovarian or testicular tissue was identified. However, 1 small focus measuring 1.8 mm in maximum dimensions of the tumor was identified. This focus was composed of large uniform, polyhedral cells separated by delicate fibrous tissue septa with associated scattered benign-appearing small-sized lymphocytes. The cells had abundant pale and eosinophilic cytoplasm containing large, centrally located vesicular round to oval nuclei. Occasional prominent eosinophilic nucleoli were noted. This neoplastic focus was devoid of any immature sertoli-like cells or cylindrical thick basement membrane structures (hyaline bodies of gonadoblastoma) or any features of gonadoblastoma. The tumor cells were immunoreactive for CD117 and placental alkaline phosphatase, whereas nonimmunoreactive for pancytokeratin (Fig. 3).

DISCUSSION

One of the differential diagnoses of gonadal dysgenesis is testicular feminization syndrome. As in our patient, she was referred to our hospital with a diagnosis of testicular feminization syndrome, which we believe was based only on the male chromosomal karyotype. However, individuals with this syndrome have a female phenotype, a blind-ended vagina, in addition to bilateral cryptorchid testes and no uterus, which was not the case in our patient (15).

Paraneoplastic syndromes are known to be defined by multiple complex symptoms. They occur in approximately 10% of patients with malignancies, but are important syndromes to consider clinically because they may be the earliest manifestation of an occult tumor, may pose significant morbidity and/or mortality, and may mimic metastatic disease and therefore complicate treatment protocols. They are classified into a broad range of syndromes according to their target organ system. The general classification includes the following categories: endocrinopathies, nerve and muscle syndromes, dermatologic disorders, osseous articular, and soft tissue. The peripheral and central nervous system is not an uncommon target for these paraneoplastic syndromes, and occasionally, the syndrome may even precede the clinical recognition of the malignant neoplasm itself. These syndromes share the findings of a paraneoplastic encephalomyelitis with specific clinical syndromes reflecting the anatomic distribution of the specific target in the nervous system. They are generally subdivided into paraneoplastic cerebellar degeneration, limbic encephalitis, subacute sensory neuropathy, and eye movement disorders. The most frequent malignancy associated with these central and peripheral nervous syndromes is small cell carcinoma of the lung. Most of these syndromes are diagnosed clinically, some of which can be confirmed chemically by the isolation of certain tumor markers or specific antigens. The *anti-Ma2*-associated

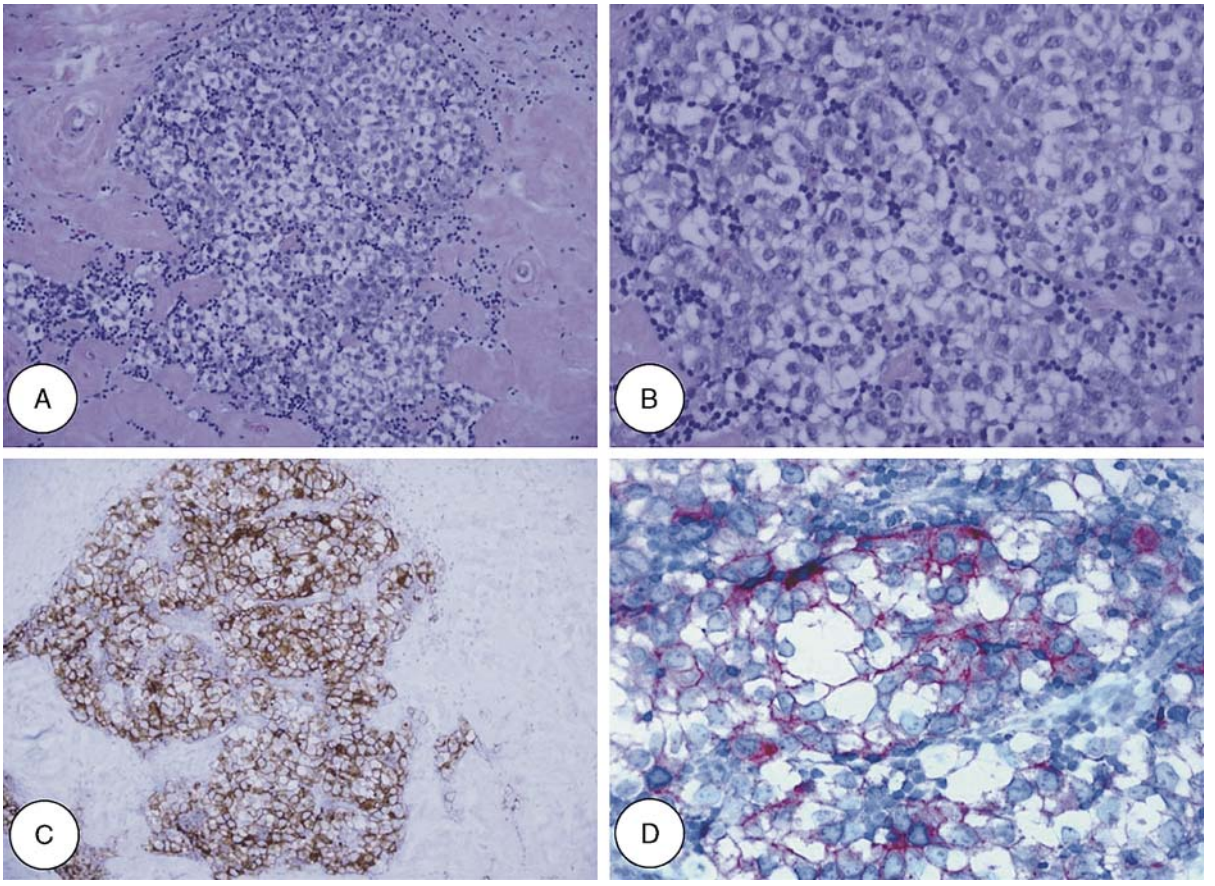

FIG. 3. A composite photomicrograph of the microscopic dysgerminoma focus: (A) and (B) on low-power and high-power magnification (hematoxylin and eosin). By immunohistochemistry, the tumor cells are positive for placental alkaline phosphatase (C) and CD 117 (D).

paraneoplastic encephalitis is one of the limbic paraneoplastic encephalopathies that are associated with positive serum or cerebrospinal fluid for *anti-Ma2* antigen. Dalmau and colleagues studied the clinical findings of 38 patients with *anti-Ma2*AE. According to the study, the most frequent primary tumor site is the testis (16). Although both seminomatous germ cell tumors and nonseminomatous germ cell tumors are associated with this disorder, the latter is more predominant. Among their 18 patients with *anti-Ma2*AE due to testicular tumors, 12 patients were nonseminomatous, 4 were seminomatous, and 2 were found to have only carcinoma *in situ*.

In paraneoplastic neurological syndromes, the primary tumor is often small and difficult to identify, a feature that has been attributed to a possible antitumor effect. In our patient, there was a very small microscopic focus of dysgerminoma with an extensive background of sclerosis and fibrosis. It is uncertain at this juncture as to whether these scarred areas were originally tumor masses and had undergone some sort of sclerosing-type degeneration.

The pathogenesis of these neurological syndromes is not fully understood. Some investigators hypothesize that certain tumors secrete certain proteins that may trigger an autoimmune response against different components of the nervous system. Therefore the presence of *anti-Ma2* antibodies together with appropriate clinical findings should prompt every effort to find an underlying malignancy, specifically lung carcinoma and germ cell tumor. In our case, a vigorous attempt has been made to identify an occult neoplasm, and only a tiny focus of dysgerminoma had been identified in the adnexal mass. As we described in our case, only 1 microscopic focus was found with viable and histologically recognized dysgerminoma, whereas the rest of the mass was composed of vast areas of scar tissue and fibrosis with dystrophic calcifications.

We can only speculate that these histologic findings stem from multiple pathogenetic pathways. First, it

could represent spontaneous regression of the vast majority of primary germ cell tumor and the mechanism of this regression is not known. Second, a vigorous immune response or ischemia caused by the neoplasm outgrowing its own blood supply triggered these histologic findings. Third, there could have been a gonadoblastoma element that underwent sclerosis or regression (burned out) where only 1 focus of germ cells survived.

Whatever the pathogenesis of development of fibrosis and sclerosis, it is well known that these sclerotic and fibrotic areas (burned out areas) can always invite dystrophic calcification similar to our case (17–20).

In conclusion, early recognition of these paraneoplastic clinical syndromes should prompt a thorough and meticulous search for occult neoplasms. These occult neoplasms are more common in patients with gonadal dysgenesis syndromes as seen in our patient. In addition, *anti-Ma2* paraneoplastic encephalitis can be an early manifestation of gonadal germ cell tumor, where a thorough search is highly recommended.

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