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Paraneoplastic Syndromes Associated with Ovarian Teratomas - Systematic Review

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ABSTRACT

Ovarian teratomas are germ cell tumors characterized by their ability to differentiate into tissues derived from all three embryonic germ layers. Although most teratomas are benign, particularly mature cystic teratomas, they may be associated with a wide spectrum of paraneoplastic syndromes. These syndromes are not caused by the direct presence of the tumor but rather by immune-mediated or hormonal mechanisms triggered by the neoplasm. The most well-

recognized association is anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, although other neurological, hematological, and systemic manifestations have also been described.

This systematic review aims to analyze the types of paraneoplastic syndromes associated with ovarian teratomas, their pathophysiology, clinical presentation, and diagnostic significance. Particular attention is given to neurological autoimmune syndromes, which often precede tumor diagnosis and may serve as an early clinical indicator of an underlying neoplasm. Understanding these associations is essential for timely diagnosis and appropriate management, which frequently involves a combination of tumor resection and immunotherapy.

Background. Ovarian teratomas are germ cell tumors that may be associated with paraneoplastic syndromes, which are immune-mediated conditions often preceding tumor diagnosis and significantly affecting clinical outcomes.

Aim. The aim of this study was to systematically review paraneoplastic syndromes associated with ovarian teratomas and assess their diagnostic and clinical significance.

Material and methods. A literature review was conducted based on available scientific publications concerning ovarian teratomas and related paraneoplastic syndromes, with particular focus on neurological and autoimmune manifestations.

Results. The most common paraneoplastic syndrome associated with ovarian teratomas is anti-NMDAR encephalitis. Other reported conditions include autoimmune hemolytic anemia, neuromyelitis optica spectrum disorder, and GFAP-associated astrocytopathy. These syndromes are primarily immune-mediated and may precede tumor detection.

Conclusions. Paraneoplastic syndromes may serve as early indicators of ovarian teratomas. Early diagnosis and combined treatment, including tumor resection and immunotherapy, are crucial for improving patient outcomes.

Keywords: ovarian teratoma, paraneoplastic syndromes, anti-NMDAR encephalitis, autoimmune disorders, germ cell tumors, mature teratoma, immature teratoma

1. Introduction

A teratoma is a tumor derived from pluripotent germ cells. It arises through the uncontrolled growth and differentiation of these cells into all germ layer lines – ectoderm, endoderm, and mesoderm. These tumors do not have a uniform histological structure, but rather constitute a mixture of various, intermingled tissues. (1–4)

In many cases, these tissues can include highly differentiated structures such as skin, hair follicles, cartilage, bone, and even neural tissue, reflecting the remarkable differentiation potential of germ cells. (1,4) The diversity of tissue types found within teratomas contributes to their complex biological behavior and variable clinical presentation. (4–6)

Paraneoplastic syndromes are a group of symptoms accompanying the growth of cancer, which do not result from its physical presence but are instead the consequence of the body's immune response or ectopic secretion of biologically active substances. (7–9) Their presence may result from the tumor's secretion of hormones, cytokines, or immune-mediated mechanisms, and the manifestation of endocrine, neurological, or hematological abnormalities often precedes the diagnosis of cancer. (7,8,10–12) Therefore, increasing awareness of paraneoplastic syndromes is crucial to expedite diagnosis. In this work, attention is paid to the analysis of the types of paraneoplastic syndromes and their diagnostic significance. (13–15)

Moreover, recognizing these syndromes can significantly improve patient outcomes, as early identification of an underlying tumor often allows for prompt treatment and reduction of complications.(8,16)

Research Objective

The objective of this study is to systematically review and analyze the spectrum of paraneoplastic syndromes associated with ovarian teratomas, with particular emphasis on their pathophysiology, clinical presentation, and diagnostic significance. Additionally, the study aims to evaluate the relationship between different types of teratomas and the occurrence of specific paraneoplastic manifestations, as well as to highlight the importance of early recognition of these syndromes in clinical practice. The review also seeks to assess current therapeutic approaches and their effectiveness in improving patient outcomes.

Research Problems

What types of paraneoplastic syndromes are most commonly associated with ovarian teratomas?

What are the underlying immunological and molecular mechanisms responsible for the development of these syndromes?

To what extent can paraneoplastic syndromes serve as early indicators of ovarian teratomas?
How do different types of teratomas (mature vs. immature) influence the occurrence and severity of paraneoplastic manifestations?
What is the impact of early tumor detection and treatment on the prognosis of patients with paraneoplastic syndromes?

Research Hypotheses

Paraneoplastic syndromes associated with ovarian teratomas are predominantly immune-mediated and result from cross-reactivity between tumor antigens and normal tissues, particularly within the nervous system.
Anti-NMDAR encephalitis is the most common and clinically significant paraneoplastic syndrome associated with ovarian teratomas.
Paraneoplastic syndromes often precede the diagnosis of ovarian teratomas and may serve as an early diagnostic marker of the disease.
Early detection and surgical removal of ovarian teratomas significantly improve neurological and systemic outcomes in patients with paraneoplastic syndromes.
The type and histological characteristics of the teratoma influence the likelihood and type of associated paraneoplastic manifestations.

2. Research materials and methods

This study was conducted as a systematic review of the available literature focusing on paraneoplastic syndromes associated with ovarian teratomas. The analysis included original research articles, case series, and selected case reports published between 2000 and 2026, in order to ensure up-to-date and clinically relevant data. A comprehensive literature search was performed using electronic databases such as PubMed, Google Scholar. The search strategy was based on a combination of predefined keywords and Medical Subject Headings (MeSH) terms, including: *“ovarian teratoma,” “paraneoplastic syndrome,” “anti-NMDAR encephalitis,” “autoimmune encephalitis,” “neuromyelitis optica spectrum disorder,” “GFAP astrocytopathy,”* and *“autoimmune hemolytic anemia.”* Boolean operators (AND, OR) were used to refine the search and improve the specificity of results. Inclusion criteria comprised studies published in English, involving human subjects, and directly addressing the relationship between ovarian teratomas and paraneoplastic syndromes. Particular emphasis was placed on studies describing clinical presentation, pathophysiology, diagnostic approaches, and treatment outcomes. Exclusion criteria included studies not related to ovarian teratomas, articles lacking

full-text availability, duplicate records, and publications with insufficient clinical data. The selection process involved an initial screening of titles and abstracts, followed by full-text evaluation of eligible articles. Data extracted from the selected studies included patient demographics, type of teratoma, type of paraneoplastic syndrome, diagnostic findings, treatment strategies, and clinical outcomes. The collected data were analyzed qualitatively, with a focus on identifying common patterns, mechanisms, and clinically significant associations between ovarian teratomas and paraneoplastic syndromes.

2.1. AI.

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. **AI** were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

3. Research results

3.1. Ovarian Teratoma – Characteristic

Ovarian teratomas are divided into mature and immature forms. (1,3) The exact etiology of these tumors remains unclear, although several hypotheses suggest genetic, hormonal, and environmental influences. Reported risk factors include late menarche, prolonged irregular menstrual cycles, a history of cystic teratoma, reduced parity, infertility, excessive alcohol consumption, and physical activity. (2) These factors may influence hormonal balance or ovulatory patterns, potentially contributing to tumor development. (1–3) Recent studies have demonstrated that the cellular origin of mature teratomas is diploid, meaning they contain sets of homozygous alleles. Analysis of polymorphic markers revealed a homozygous pattern in teratoma components, supporting their parthenogenetic origin from germ cells following meiosis. This suggests that teratomas may arise from oocytes that undergo abnormal activation

without fertilization. (2,4–6,17) Malignant transformation occurs in approximately 0.5–3% of all cases. (1) This phenomenon most frequently affects tumors larger than 10 cm in diameter and is more common in patients over 45 years of age. In 80% of cases, the malignancy manifests as squamous cell carcinoma, reflecting the predominance of ectodermal components in these tumors. In approximately 7% of cases, adenocarcinoma develops. (5,6) Other rare forms of malignant transformation include melanoma, carcinoid tumors, and thyroid carcinoma, particularly in specialized variants such as struma ovarii. (4,18)

Table 1. Classification of ovarian teratomas with malignant transformation according to the type of neoplastic component (own elaboration based on the literature)

type 1	teratoma with a component of another germ cell tumor
type 2	teratoma with a cancer component
type 3	teratoma with sarcoma component
type 4	teratoma with a complex malignant component

3.1.1. Mature Teratoma

Mature teratoma is the most common subtype of ovarian germ cell tumors, accounting for 11% of all ovarian tumors, 69% of germ cell tumors, and 95% of teratomas. The predominant form is cystic, commonly referred to as a dermoid cyst. These cysts typically contain well-differentiated tissues such as skin, hair, neural tissue, and sebaceous material, giving them a characteristic appearance. (1,4,6) They are usually asymptomatic, although some patients may present with nonspecific symptoms such as pelvic discomfort, abdominal fullness, or acute pain due to complications like ovarian torsion or rupture. Therefore, most cases are detected incidentally during imaging studies. (1,2) In some instances, complications such as infection or rupture can lead to an acute abdomen, requiring urgent surgical intervention. (1) In about 10% of cases, they occur bilaterally, and their diameter usually does not exceed 10 cm. Imaging studies may reveal a Rokitansky protuberance, a solid projection into the cyst cavity that often contains hair or calcified structures such as teeth. (5) The most common type of

mature teratoma is a dermoid cyst, which contains predominantly ectodermal components. It can secrete thyroid hormones and serotonin. (4,6) This hormonal activity, although uncommon, may lead to clinical symptoms such as hyperthyroidism or carcinoid-like syndromes. (6) Right-sided tumors are more frequently observed than left-sided ones, although the reason for this asymmetry remains unclear and may be related to anatomical or vascular differences.

3.1.2. Immature Teratoma

An immature teratoma is a malignant germ cell tumor composed of tissues derived from all three germ layers, with the presence of immature or embryonal elements. It occurs more frequently in young women and is the second most common malignant germ cell tumor after dysgerminoma. It is also unique among germ cell tumors in that it is histologically graded. (3,17) Although there is no universal consensus regarding optimal therapeutic management, the prognosis is generally favorable, with high survival rates and good potential for fertility preservation. It is significantly rarer than the mature form. (3,6) Histologically, immature teratomas contain varying amounts of immature tissue, most commonly neuroepithelial tissue, which is a key determinant of tumor grade and prognosis. The most commonly affected individuals are adolescents and young adults of reproductive age, highlighting the importance of fertility-preserving treatment strategies. (3,5,6) Imaging studies typically reveal heterogeneous masses with mixed echogenicity, including solid components, cystic areas, and calcifications. (1,3) These tumors may also exhibit rapid growth and a tendency to spread beyond the ovary, necessitating careful staging and management. (3) They may secrete chorionic gonadotropin, which can serve as a useful tumor marker in diagnosis and monitoring response to therapy. (6)

Table 2. Comparison of mature and immature ovarian teratomas (own elaboration based on the literature)

Feature	Mature teratoma	Immature teratoma
Nature	Benign	Malignant
Age group	20-40 years	<20years
Histology	Well-differentiated tissues from at least two germ layers	Presence of immature (embryonal) tissues,

		especially neuroectoderm
Clinical course	Slow-growing, often asymptomatic	More aggressive
Frequency	Most common ovarian germ cell tumor	Rare
Treatment	Surgical removal	Chemotherapy + surgery

3.1.3. Struma Ovarii

Ovarian goiter (struma ovarii) is a specialized form of teratoma predominantly composed of thyroid tissue. It may present with clinical features of hyperthyroidism due to excessive hormone production. Imaging typically reveals a lobulated, hypervascular cystic mass, and magnetic resonance imaging may show a characteristic “stained glass” appearance. (6,18) Although most cases are benign, less than 5% undergo malignant transformation. The most common malignant forms are papillary and follicular thyroid carcinomas.

In rare cases, struma ovarii may also be associated with ascites and pleural effusion, mimicking ovarian malignancy (pseudo-Meigs syndrome). (6,18)

3.1.4. Treatment

Treatment depends on the type and stage of the teratoma. (1,3) In the case of mature teratoma, surgical removal is the treatment of choice and is associated with an excellent prognosis. Minimally invasive techniques, such as laparoscopy, are commonly used. (1,5,16) For immature teratoma, adjuvant chemotherapy is considered the standard approach. In advanced cases, neoadjuvant chemotherapy may be administered to reduce tumor burden and facilitate fertility-sparing surgery. (16) Long-term follow-up is essential, as recurrence can occur, particularly in higher-grade tumors.

3.2. Paraneoplastic Syndromes

Ovarian teratomas can be associated with a variety of paraneoplastic syndromes, which often involve the nervous system. The most well-known is anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. Other reported conditions include autoimmune hemolytic anemia, optic neuritis, myelin oligodendrocyte glycoprotein-associated encephalomyelitis, anti-

contactin-associated encephalitis, and serotonergic syndrome. (7–9) These syndromes are believed to arise due to immune cross-reactivity between tumor antigens and normal tissues, particularly neural structures. As a result, the immune system mistakenly attacks healthy cells, leading to diverse and often severe clinical manifestations. (7,8,13)

3.2.1. Anti-NMDAR Encephalitis

Anti-NMDAR encephalitis is most commonly associated with mature ovarian teratomas. It often presents before tumor diagnosis and is independent of tumor size. Patients typically develop psychiatric symptoms such as personality changes, agitation, or psychosis. (8,9) Neurological symptoms may include seizures, sleep disturbances, movement disorders, speech dysfunction, and memory impairment. (13,19) In severe cases, patients may develop autonomic instability, decreased consciousness, and require intensive care support. The pathogenesis is thought to involve antibodies targeting NMDAR receptors expressed by neural tissue within the teratoma. These antibodies cross the blood-brain barrier and disrupt normal neuronal signaling. (11) Despite severe symptoms, early tumor removal combined with immunotherapy (corticosteroids, IVIG, plasma exchange) leads to good outcomes in most cases. (7,13) Second-line therapies include rituximab and cyclophosphamide, particularly in refractory cases.

3.2.2. Autoimmune Hemolytic Anemia (AIHA)

Several cases of AIHA associated with teratomas have been reported. Proposed mechanisms include antigenic mimicry, direct antibody production by the tumor, and alteration of red blood cell antigens. (10,12,20) This condition should be considered in cases of unexplained or treatment-resistant hemolytic anemia. Surgical removal of the tumor often leads to complete resolution. (10,12,20) Early recognition is crucial to prevent severe anemia-related complications.

3.2.3. Neuromyelitis Optica Spectrum Disorder (NMOSD)

NMOSD is an autoimmune disorder characterized by inflammation of the optic nerves and spinal cord. It is associated with antibodies against aquaporin-4 (AQP4-IgG), detected in most patients. (19,21,22) Symptoms include vision loss, paralysis, sensory disturbances, and autonomic dysfunction. The immune response triggered by the tumor may lead to cross-reactivity with astrocytes, causing central nervous system damage. (19,21,22)

3.2.4. GFAP-Associated Astrocytopathy

GFAP-associated astrocytopathy is a recently identified autoimmune condition affecting the central nervous system. It is diagnosed by detecting GFAP-IgG antibodies in cerebrospinal fluid. (14,15) Clinical features include fever, headache, encephalopathy, and movement disorders. About 25% of patients have an associated neoplasm, most commonly a teratoma. (14,15) The coexistence of multiple antibodies suggests a complex and multifactorial immune response.

4. Discussion

The present review highlights the complex and multifaceted relationship between ovarian teratomas and paraneoplastic syndromes, emphasizing their important diagnostic and clinical implications. Although ovarian teratomas are most often benign, especially in the case of mature cystic teratomas, their ability to trigger systemic immune-mediated responses demonstrates that their clinical impact extends beyond local tumor effects. (7)

A key observation is the predominance of neurological paraneoplastic syndromes, particularly anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. (8,9) This association appears to be strongly linked to the presence of neural tissue within teratomas, which may act as a source of antigens that trigger an autoimmune response. The concept of antigenic mimicry and cross-reactivity between tumor-derived antigens and central nervous system structures is supported by multiple studies. (8,10,21) The involvement of B-cell-mediated humoral immunity further strengthens this hypothesis and explains the effectiveness of immunotherapy in many cases. (16,23)

An important clinical aspect is that paraneoplastic syndromes frequently precede the diagnosis of ovarian teratomas. This significantly increases their value as early diagnostic indicators. (13) However, the nonspecific and often psychiatric nature of initial symptoms may lead to misdiagnosis or delayed recognition. (19) This issue underlines the need for greater awareness among clinicians, particularly neurologists and psychiatrists, to consider an underlying neoplastic process in young women presenting with acute neuropsychiatric or unexplained neurological symptoms. (13)

In addition to anti-NMDAR encephalitis, this review identifies several less common syndromes, including autoimmune hemolytic anemia, neuromyelitis optica spectrum disorder (NMOSD), and GFAP-associated astrocytopathy. (10,14,21) Although rare, these conditions confirm the heterogeneity of immune responses associated with teratomas. The coexistence of multiple autoantibodies in some patients suggests that the underlying mechanisms are complex

and may involve multiple immunological pathways rather than a single antigen-antibody interaction. (13)

Interestingly, the relationship between tumor type and the occurrence of paraneoplastic syndromes appears to be independent of malignant potential. (5,16) Mature teratomas, despite being benign, are more frequently associated with autoimmune neurological disorders. This suggests that tissue composition, particularly the presence of differentiated neural elements, plays a more significant role than tumor aggressiveness in triggering immune responses. (7)

The findings also emphasize the importance of early diagnosis and prompt surgical intervention. Early tumor removal, combined with immunotherapy, has been shown to significantly improve patient outcomes and reduce the risk of recurrence. Conversely, delayed diagnosis may result in prolonged disease progression and increased morbidity. (13,16) However, several limitations must be acknowledged. The rarity of many of the described syndromes limits the availability of large-scale studies, with most data derived from case reports and small case series. This heterogeneity makes it difficult to establish standardized diagnostic and treatment guidelines. Furthermore, variability in clinical presentation and reporting may contribute to underdiagnosis or misclassification of these conditions. (7)

Future research should focus on elucidating the precise immunological mechanisms involved, identifying specific tumor antigens, and developing targeted therapeutic strategies. Larger, multicenter studies are necessary to improve the evidence base and optimize patient management.

5. Conclusions

Ovarian teratomas are an important but often underrecognized cause of paraneoplastic syndromes, particularly those affecting the nervous system. Paraneoplastic manifestations, especially anti-NMDAR encephalitis, may precede tumor diagnosis and serve as critical early clinical indicators. The development of these syndromes is primarily driven by immune-mediated mechanisms, with a key role of antigenic cross-reactivity between tumor tissues and normal structures. Early detection and prompt surgical removal of the tumor, combined with appropriate immunotherapy, are essential for improving patient outcomes and reducing the risk of long-term complications. Increased clinical awareness and a multidisciplinary approach are crucial for timely diagnosis and effective management of patients with suspected paraneoplastic syndromes associated with ovarian teratomas.

Disclosure

The authors declare no conflict of interest.

Supplementary Materials

Not applicable.

Author's Contributions

Conceptualization WK, AK; methodology SK,LK; data curation, MK,KK; writing—original draft preparation WK, LK and AK; writing—review and editing KK; supervision MK, SK. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

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