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REVIEW

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Autoimmune encephalitis and paraneoplastic encephalitis: difficulties in diagnosis and management in the ICU

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Abstract

Autoimmune encephalitis (AIE) represents a category of relatively newly described neurological disorders associated with an increasing prevalence, a significant impact on the healthcare system, and a high rate of intensive care unit (ICU) admission. This category of diseases often requires prompt treatment, even before a definitive diagnosis is established. In the ICU, patients present with nonspecific signs and symptoms for AIE, which pose challenges in both management and diagnosis. Patients frequently exhibit dysautonomia, severe physical and psychic agitation, as well as tremors and dyskinesia, all of which complicate the diagnosis. They are prone to developing infections, including ventilator-associated pneumonia, and issues related to difficult venous access and pressure ulcers. Early initiation of immunosuppressive treatment is necessary to improve patients' outcome. Through this article, we aimed to summarize current knowledge in terms of the difficulties in diagnosing and management of this pathology in the ICU, as well as the implications for the healthcare system in terms of human and financial resources.

Keywords: encephalitis, autoimmune, paraneoplastic, immunotherapy, ICU.

Introduction

Encephalitis represents the inflammation of the brain associated with frequent damage to the cerebral cortex. Due to the difficulty in diagnosis, until the beginning of the present century, encephalitis was predominantly considered to be infectious. In recent years, so-called autoimmune encephalitis (AIE) has begun to equal infectious encephalitis in incidence and prevalence. Initially, they were classified as paraneoplastic syndromes and described as limbic encephalitis. Subsequently, antibodies against intracellular or cell surface structures were found in both plasma and cerebrospinal fluid (CSF). The discovery of new antibodies has led to the dichotomization of encephalitis into autoimmune and paraneoplastic. Thus, AIE is associated with antibodies against surface or synaptic structures, such as anti-*N*-methyl-D-aspartate receptor (NMDAr), anti-leucine-rich glioma-inactivated 1 (LGI1), anti-contactin-associated protein-like 2 (CASPR2), anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAr), anti-gamma-aminobutyric acid (GABA-A, GABA-B), anti-neuronal cell adhesion protein (IgLON5), anti-dipeptidyl-peptidase-like protein 6 (DPPX), anti-glycine receptor (GlyR) or intracellular structures also called onconeural antibodies [anti-Hu, anti-Ma2, anti-collapsin response-mediator protein 5 (CRMP5)] [1–3].

Autoimmune and paraneoplastic encephalitis is a group of diseases with an incidence of 0.8–1.2/100 000 people, not very different from the incidence of infectious encephalitis ~1/100 000 people. It is also associated with very high costs, especially if the treatment requires hospitalization in the intensive care unit (ICU) (~$50 000 per hospitalized case on the general ward compared to ~$170 000 in more severe cases requiring intensive care management) [4, 5].

Diagnosis of encephalitis

The diagnosis of most encephalitis, regardless of their autoimmune or paraneoplastic etiology, is made based on specific antibodies associated with a clinical picture. The problem occurs when specific antibodies are negative. To overcome this issue, international academic societies have proposed different diagnostic criteria. Thus, a neurological syndrome with subacute (up to three months) and progressive clinical picture, bilateral lesions on magnetic resonance imaging (MRI) in T2-weighted fluid-attenuated inversion recovery (FLAIR) signal, electroencephalography (EEG) changes with epileptiform appearance or reduced activity in both temporal lobes and pleocytosis in the CSF are simultaneously required for the diagnosis after exclusion of any other causes [6–8].

Patients with suspected AIE should be thoroughly investigated. Neurological examination, cerebral imaging and serological tests must be assessed early to make a timely diagnosis for appropriate treatment initiation, as any delay in diagnosis has been associated with unfavorable outcome. The most recommended paraclinical tests are EEG, MRI, CSF.

Electroencephalography

Routinely performed in neurological patients, EEG is very useful in differentiating from nonconvulsive epileptic

seizures. The most frequently found changes in patients with AIE on the EEG are focal or generalized epileptiform activity (usually in the temporal lobes) or, on the contrary, a very low neuronal activity. In one third of cases (associated with anti-NMDAr antibodies), "extreme delta brush" on the EEG has been observed [9–11].

Magnetic resonance imaging

MRI represents an invaluable diagnostic procedure in the differential diagnosis of neurological symptoms, as it can exclude vascular lesions or brain metastases. The downfall of the investigation is that cerebral lesions encountered in patients with AIE are not specific. They may present as hypersignal lesions in FLAIR or T2 in the temporal, cortical/subcortical, diencephalic, cerebellar lobes, as lesions in the *pons* and *medulla oblongata* or meningoencephalitic lesions [10, 12].

Cerebrospinal fluid

CSF should be analyzed for cell counts, proteins, glucose, and inflammatory markers, such as oligoclonal bands. The collected CSF specimens, together with patients' plasma, must also be sent to specialized centers to be tested for antibodies associated with AIE. At the same time, bacterial cultures, and a polymerase chain reaction (PCR) test should be used to exclude viral or bacterial encephalitis. In AIE, CSF assay shows pleocytosis with predominantly lymphocytic, moderately elevated proteins, and indexed immunoglobulin G (IgG) and oligoclonal bands in large amounts. Unfortunately, all these changes have high specificity but low sensitivity.

Pathophysiological findings

The histopathological (HP) changes are nonspecific and are associated with immune-mediated neuronal destruction. Most often, degenerative changes are present in the cerebellum, characterized by the loss of Purkinje cells and preservation of the cerebral cortex structure. Other HP aspects include gliosis and astrocytic reaction. Usually, the inflammatory reaction is not prominent, but lymphocytes and plasma cells can be identified, especially in the leptomeninges. Neoplastic encephalomyelitis is characterized by neuronal loss with marked gliosis and astrocytic reaction. It presents an inflammatory infiltrate in the meninges, as well as in the grey matter.

Differential diagnosis

Differential diagnosis is a major criterion in the definition of AIE. Thus, different etiologies for acute encephalitis, such as infectious (viral, bacterial, fungal encephalitis, tuberculosis, Creutzfeldt–Jakob disease), metabolic and toxic (Ketamine, organophosphorus, carbon dioxide, Wernicke disease, neuroleptic malignant syndrome), vascular, degenerative, inflammatory, psychiatric, mitochondrial diseases, and malignancy must be excluded [1, 3, 13, 14].

There are several types of clinical syndromes, such as limbic encephalitis and brainstem encephalitis. Limbic encephalitis can mimic the symptoms of metastatic disease affecting the brain or leptomeninges, viral encephalitis, Creutzfeldt–Jakob disease, ischemic and hemorrhagic cerebrovascular disease, Whipple disease, psychiatric disease, toxic-metabolic encephalopathy, Wernicke encephalopathy, and primary degenerative dementia. Brainstem encephalitis differential diagnosis is most commonly made with multiple sclerosis, Behçet syndrome, *Listeria* infection, enterovirus, and tuberculosis infection.

Paraneoplastic encephalitis

It represents an entity that has been the basis for all AIE. Initially, all non-infectious encephalitis were considered to be part of paraneoplastic syndrome. The clinical and paraclinical diagnosis is similar to that of AIE, with the exception that antibodies in the CSF are directed against intracellular structures, classically referred to as onconeural antibodies.

Limbic encephalitis

Limbic encephalitis represents an inflammation of the limbic system (hippocampus, hypothalamus, amygdala, cingulate gyrus, and limbic cortex). Although it is classified, especially in the initial phases of the disease, as paraneoplastic syndrome, in more than half of the cases there are no clinical or imagistic criteria to indicate the presence of a malignancy [15, 16].

Clinically, it is characterized by acute and subacute onset of symptoms including psycho-behavioral changes, neurocognitive disorders, short-term memory impairment and focal epileptic seizures with or without impairment of consciousness [17]. Paraclinically, CSF examination reveals high protein levels, glycorrhachia, pleocytosis with lymphocytic predominance, and oligoclonal bands. EEG changes include unilateral or bilateral epileptiform type activity in the temporal lobes, or slow wave type changes in the same territory. MRI examination reveals hypersignal FLAIR and T2 lesions in the limbic system. All these changes are nonspecific [10].

Limbic encephalitis is most often associated with small cell lung cancer (SCLC), thymoma, seminoma, breast cancer and Hodgkin's lymphoma.

Seminoma

Seminoma is the most common malignant germ cell tumor (GCT) of the testis. It usually affects adults, presenting with unilateral, symmetric, non-distorted enlargement of the testis. Microscopically, it consists of a proliferation of medium sized cells, with well-defined borders, with clear or eosinophilic cytoplasm, polygonal nucleus with one or more prominent nucleoli. Architecturally, it can present various patterns, such as solid sheets, nests, pseudotubules. The testicular parenchyma is atrophic or can be completely replaced by the neoplastic cells [18]. The prognosis is relatively favorable for localized tumors, and standard treatment consists of orchiectomy followed by clinical and paraclinical follow-up. In advanced stages, radiotherapy and chemotherapy have been applied and were associated with good outcomes. (Figure 1). Seminoma paraneoplastic encephalitis is most commonly associated with anti-Hu, anti-Ma2 and other types of antibodies in the CSF [19].

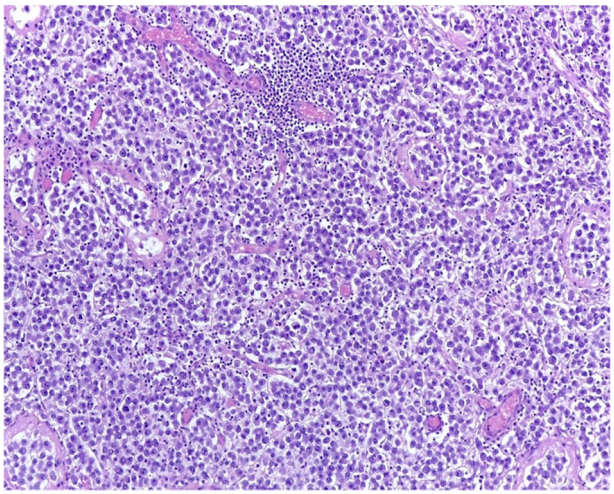

Figure 1 – ***Seminoma of the testis: malignant tumor proliferation comprising atypical germ cells with clear cytoplasm and indistinct borders. Hematoxylin–Eosin (HE) staining, ×100. With courtesy of Adrian Dumitru, MD, PhD, Department of Pathology, Emergency University Hospital of Bucharest, Romania.***

Brain stem predominant encephalitis (rhombencephalitis)

Even though most cases of paraneoplastic encephalitis do not present a single tropism, but a multitude of lesions from the limbic system to the cortex to the cerebellum to the brainstem, there are cases which present with single lesions in the brainstem and associate specific clinical picture. Most frequently, patients present with manifestations caused by damage to the brainstem nuclei and cranial nerves, such as opsoclonus, nystagmus, dysphagia, dysarthria, vertigo, central hypoventilation syndrome.

Anti-Hu antibodies are prevalent in lower brainstem damage, and anti-Ma antibodies are more common in upper damage. Also, this type of encephalitis is associated with SCLC, testicular teratoma, prostate adenocarcinoma and renal cancer [20].

Small cell lung cancer

SCLC is a malignant neuroendocrine neoplasm with an extremely aggressive natural history, usually located in the hilum of the lungs. Microscopically, it consists of sheets of atypical cells with dark-stained nuclei, without prominent nucleoli and with scant cytoplasm and high mitotic count. Necrotic areas and apoptotic bodies are often encountered. Immunohistochemically, it expresses neuroendocrine markers, such as chromogranin, synaptophysin and cluster of differentiation (CD)56. Although extremely sensitive to radiotherapy and chemotherapy, recurrence occurs frequently, and metastasis is often present regardless of the size of the primary tumor (Figures 2 and 3).

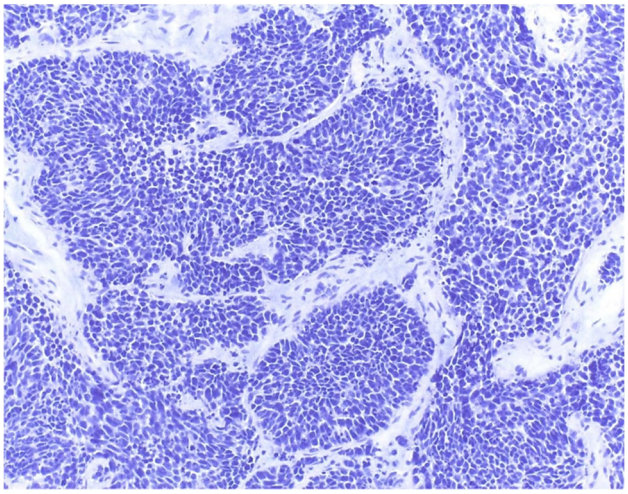

Figure 2 – ***Small cell lung cancer (SCLC): malignant tumor proliferation comprising sheets of small, round-oval cells with scant cytoplasm and molded nuclei with fine chromatin. HE staining, ×100. With courtesy of Adrian Dumitru, MD, PhD, Department of Pathology, Emergency University Hospital of Bucharest, Romania.***

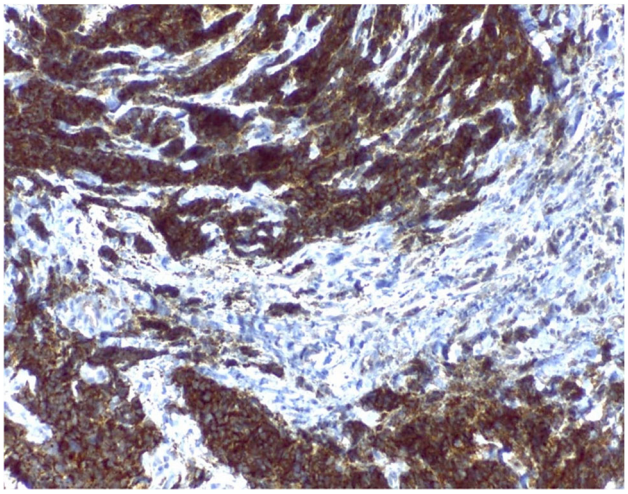

Figure 3 – ***Strong cluster of differentiation 56 (CD56) expression in SCLC. Immunohistochemistry (IHC) staining with 3,3'-Diaminobenzidine (DAB) chromogen, ×100. With courtesy of Adrian Dumitru, MD, PhD, Department of Pathology, Emergency University Hospital of Bucharest, Romania.***

For immunohistochemistry assay, the paraffin blocks are sliced using the microtome, resulting in 3 μm thick sections. The sections are subsequently mounted on slides coated with poly-L-lysine. Following that, toluene and alcohol successive baths (one hour – 15 minutes for each bath) are necessary to deparaffinize the sections. The next process performed is to rehydrate the sections by using three alcohol baths, decreasing the concentration each time (96% first time, then 80% and 70%), followed by a distilled water bath for 10 minutes. The succeeding step is to wash the slides in phosphate-buffered saline, then incubate them with normal serum for 20 minutes and, after that, with the primary antibody overnight. During the process, the Dako Labeled Streptavidin–Biotin (LSAB) is used. This is followed by carbonate buffer washing and development in 3,3'-Diaminobenzidine (DAB) hydrochloride/hydrogen peroxide. The final step involves counterstaining the nuclei with Mayer's Hematoxylin to confirm the diagnosis.

Myelitis and encephalomyelitis

It is a condition that can be located anywhere throughout the nervous system: limbic system, brainstem, cerebellum, spinal cord, and autonomic nervous system. Pathological examination reveals perivascular and interstitial inflammatory infiltrates with T-lymphocytes, gliosis in response to central nervous system damage and signs of neuronal death. It is most commonly associated with anti-Hu antibodies, SCLC and, in most cases, the malignancy is difficult to diagnose especially in early stages [21].

Autoimmune encephalitis

AIE refers to acute or subacute, progressive inflammation of the brain associated with antibodies against neuronal cell surface and synaptic protein, most commonly being anti-NMDAr encephalitis. There are several types of AIE, depending on the type of antigen. The diagnostic criteria of certainty are represented in Table 1.

Table 1 – ***Diagnostic criteria of certainty autoimmune encephalitis (all four at the same time)***

1. Subacute evolution (rapid progression less than three months) of neurological and psychiatric manifestations.
2. Bilateral temporal lobe lesions on T2 FLAIR MRI.
3. Pleocytosis in CSF or EEG changes in the temporal lobes of epileptiform type or reduced neuronal activity.
4. Exclusion of other alternative cause.

CSF: Cerebrospinal fluid; EEG: Electroencephalogram; FLAIR: Fluid-attenuated inversion recovery; MRI: Magnetic resonance imaging.

Anti-NMDAr autoimmune encephalitis

It is a relatively new entity first described in 2007, and currently ranks first in incidence of immune-mediated encephalitis. It is more common in females (women to men ratio of 8:2) during the second decade of life [9, 22–24].

The disease presents initially with a flu-like prodrome, followed within a few days by neurological and psychiatric symptoms, such as anxiety, agitation, hallucinations, psychotic episodes, sleep disorders (initially insomnia and then hypersomnia during late stages), memory disorders, epileptic seizures, altered consciousness up to deep coma, catatonic states alternating with severe agitation, dyskinesias (orofacial, choreoathetosis, ballistic, dystonia) and dysfunction of the autonomic nervous system (tachycardia or bradycardia, hyperthermia, hemodynamic alterations) [25, 26].

Paraclinical examination is crucial for the correct diagnosis. CSF assay reveals pleocytosis with predominantly lymphocytic and oligoclonal bands (even though these changes may be missed in the early stages). The EEG shows classical epileptiform changes, or reduction of focal or generalized neuronal activity. However, electrophysiological changes are nonspecific, but may have a role in the differential diagnosis of nonconvulsive *status epilepticus*. As previously mentioned, in AIE with anti-NMDAr antibodies, "extreme delta brush" has been reported in one third of patients. MRI changes are non-specific and can show lesions at any level of the nervous system [27]. The diagnosis is confirmed by IgG anti-GluN1 (NMDAr subunit) antibodies identified in the CSF. Plasma antibodies are not useful, as they may be absent giving a false negative result [28, 29].

This type of encephalitis is commonly associated with malignancy. Thus, ovarian teratoma is the most common type of cancer in females and, if appropriate surgical management is undertaken, is associated with a satisfactory outcome and a favorable long-term survival. In men, the association with malignancy is rarer and is represented mostly by testicular germinoma, SCLC and Hodgkin's lymphoma.

Teratoma

Histopathologically, it is a GCT which consists of well-differentiated derivates of the three germ layers. The ectodermal component, the most frequently encountered, is represented by nervous tissue, squamous epithelium, and dermal appendages. The mesodermal component is represented by bone, cartilage, smooth muscle, fibrous and fatty tissue. The endodermal component is represented by gastrointestinal and bronchial epithelium, thyroid, salivary glands [30]. The subunits of NMDAr targeted by antibodies are expressed in the neural and/or squamous tissue of the associated teratomas (Figures 4 and 5).

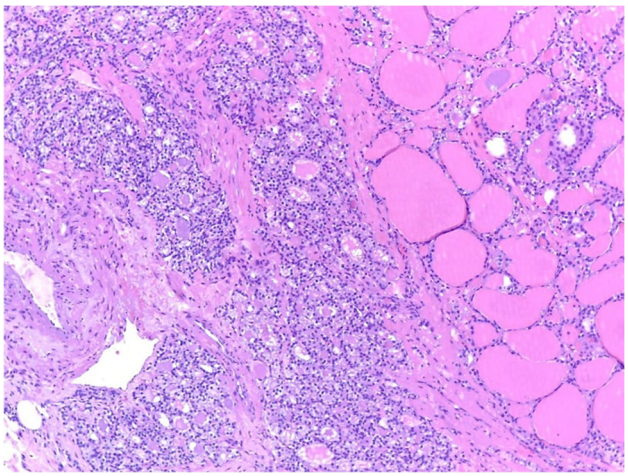

Figure 4 – ***Mature teratoma of the ovary comprising thyroid follicular epithelium. HE staining, ×200. With courtesy of Adrian Dumitru, MD, PhD, Department of Pathology, Emergency University Hospital of Bucharest, Romania.***

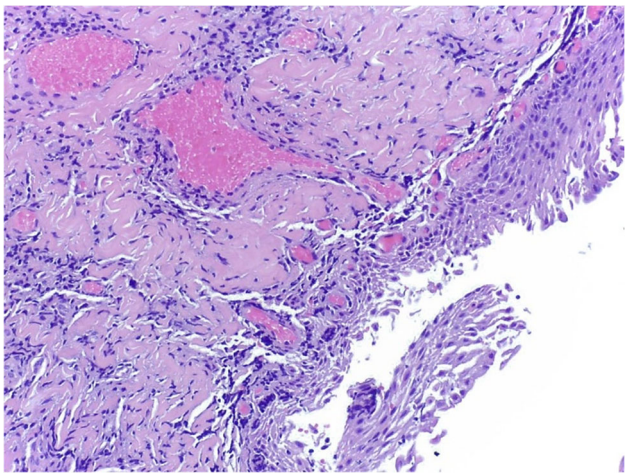

Figure 5 – ***Mature teratoma of the ovary displaying cystic fibro-vascular wall lined by non-keratinizing stratified squamous epithelium. HE staining, ×100. With courtesy of Adrian Dumitru, MD, PhD, Department of Pathology, Emergency University Hospital of Bucharest, Romania.***

Treatment consists of immunosuppression and tumor resection when appropriate. There is no consensus as to when to initiate treatment. In most cases, the first line of treatment is started with Methylprednisolone 1 g per day for five days in parallel with Ig 400 mg/kg/day for five days or plasma exchange (between five and 10 sessions). The choice between Ig and plasma exchange is made on a case-by-case basis depending on the physician's personal experience, as well as resource availability. Ig treatment may be associated with serious adverse events like aseptic meningitis, thromboembolic phenomena, and acute kidney injury. Plasma exchange is an extracorporeal replacement therapy that is associated with serious adverse events like electrolyte abnormalities, bleeding or thrombotic disorders, anaphylactic shock, hemodynamic compromise, and complications related to venous access [31, 32].

If, from a clinical standpoint, there are no signs of improvement in a few weeks, then the second line of treatment can be initiation and it consists of Rituximab (chimeric monoclonal anti-CD20 antibody) in a dose of 1 g every two weeks or 375 mg/m^2 weekly for four weeks or Cyclophosphamide (500–1000 mg/m^2 monthly for six months). Before initiating Rituximab treatment, screening for tuberculosis, hepatitis C and hepatitis B should be performed [33, 34]. Experimental drugs like Tocilizumab [anti-interleukin-6 (IL-6) monoclonal antibody] and Bortezomib (inhibitor of the ubiquitin-proteasome system) have been tested in small case series, but they have not yet proven their efficacy in large scale studies [35, 36].

A large proportion of patients with AIE with anti-NMDAr antibodies require ICU admission. This results in high healthcare associated costs [4]. Also, ICU admission is determined by life-threatening complications including altered consciousness with loss of airway protection and need for invasive mechanical ventilation, *status epilepticus* and refractory *status epilepticus*, increased intracranial pressure, respiratory failure, and autonomic nervous system dysfunction [37].

AIE with anti-NMDAr antibodies shows a high degree of relapse. Survivors have an approximately 20% risk of relapse in the first years. However, in such cases, rapid initial management, especially initiation of second-line therapy, is performed earlier [38] and, despite the severity of the disease, a high percentage of patients have a favorable outcome. Prognostic factors associated with a poor prognosis are represented by delay in initiating treatment, prolonged ICU length of stay, sepsis, mechanical ventilation associated pneumonia, and tracheostomy [39].

Encephalitis with anti-LGI1 antibodies

This type of encephalitis has clinical manifestations and a natural history similar to anti-NMDAr encephalitis. It has been associated most frequently with ultra-resistant *status epilepticus* and rapid eye movement (REM) sleep disturbances. EEG and MRI changes are specific for limbic encephalitis. CSF assay demonstrated pleocytosis and oligoclonal bands. The most common associated malignancy is thymoma.

Thymoma

Thymoma is a malignancy originating in the thymic epithelial cells and represents the most common tumor of the mediastinum, affecting mainly adults. Histologically, it is characterized by an encapsulated proliferation with lobular architecture, with cellular lobules separated by fibrous bands of variable thickness. The neoplastic epithelial cells are either bland and spindle or polygonal, with various number of reactive thymocytes. Based on the cytological aspects, thymomas are classified in different subtypes: A – elongated and spindle cells, B – polygonal cells, and AB – mixed cells [40]. Type B is further subclassified from B1 to B3 based on the ratio of thymocytes and tumor cells. Treatment requires a multidisciplinary approach, as it may require chemotherapy, immunotherapy, and if possible, surgical resection. Thymoma has a relatively high probability of recurrence and may possess a high risk of associated second malignancy (Figure 6).

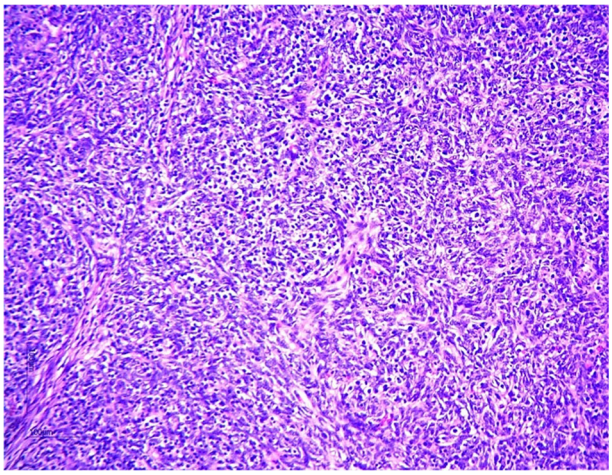

Figure 6 – ***Type AB thymoma. HE staining, ×200. With courtesy of Adrian Dumitru, MD, PhD, Department of Pathology, Emergency University Hospital of Bucharest, Romania.***

LGI1 protein is a ligand of some proteins with a pivotal role in epilepsy induction (disintegrin and metalloproteinase domain-containing protein 22 and 23). This is the reason why this type of encephalitis is more often associated with treatment-resistant epilepsy. Management consists of immunotherapy, Ig therapy, plasma exchange and Mycophenolate Mofetil. Currently, Rituximab has a limited indication. Up to 80% of patients go into remission, but one third relapse.

Encephalitis with anti-CASPR2 antibodies

Most patients present with a clinical picture of limbic encephalitis or Morvan syndrome composed of neuromyotonia, memory disorders that can lead to total memory loss, sleep, and autonomic nervous system disorders. Unlike other types of encephalitis, onset of the disease is around 65 years, and it has not been associated with malignancy except in a few cases with thymoma.

Symptoms are varied, but patients usually show three or more of the following: cognitive impairment, cerebellar damage, hyperexcitability of the peripheral nervous system,

insomnia, neuropathic pain, and weight loss. The natural history is towards a subacute disease lasting up to several months. The overall prognosis is favorable as most patients have a good response to immunosuppressive therapy.

Encephalitis with anti-AMPAr antibodies

The disease affects mainly females with an average age of 50–60 years. Clinically, it presents as limbic encephalitis and, in two thirds of cases, it is associated with a malignancy, most commonly breast, thymus or lung cancer. Current management consists of surgical removal of the tumor and immunotherapy.

Diagnostic and treatment strategy in the ICU

In the ICU, AIE can be suspected when there is a subacute neurological dysfunction with less than three months of onset. As part of the differential diagnosis, it is necessary to exclude toxic, metabolic, infectious, and paraneoplastic etiologies. Routine blood and serological tests should be performed, as well as specific ones, including antibodies assay. The most available diagnostic test is represented by cerebral computed tomography, although its sensitivity and specificity are extremely low. Continuous EEG monitoring is a straightforward and useful method for monitoring the patient's neurological status. The diagnostic "gold standard" remains contrast-enhanced cerebral MRI. Lumbar puncture with CSF analysis is the method with the highest specificity and sensitivity in detecting AIE.

AIE presents multiple management challenges for the intensivist. Agitation, shivering, and sympathetic hyperreactivity require increased attention as they can predispose to over sedation, especially in patients with pre-existing neurological deficits. Immunosuppressive treatment carries risks of adverse events that should be minimized as much as possible. Particularly, in patients requiring invasive mechanical ventilation, immunotherapy can trigger or worsen ventilator-associated pneumonia. Therefore, bacteriological screening should be conducted prior to initiating immunotherapy. The treatment of AIE is not limited to managing the underlying disease but also involves treating secondary symptoms. Mechanical ventilation should follow lung-protective strategies and appropriate titration of end-expiratory positive pressure to minimize the risk of cerebral edema. Hemodynamics should be closely monitored to maintain adequate cerebral perfusion pressure without protecting against fluid overload that can aggravate the pre-existing neurological dysfunction. In severe cases, a multidisciplinary approach should be undertaken by intensivists, neurologists, and neurosurgeons to minimize cerebral injury.

Conclusions

AIE is increasingly encountered in ICU patients and is associated with a high morbidity and mortality, a prolonged ICU length of stay, and significant healthcare associated costs. With early diagnoses and appropriate management, it has been associated with a high incidence of remission. Besides early initiation, the treatment should be tailored to specific types of encephalitis based on paraclinical tests and especially antibody assays. Although further research is still needed to fully understand this panel of diseases, advancements in the field of molecular medicine have made it possible to improve the quality of life and reduce mortality of patients with AIE.

Conflict of interests

The authors declare that they have no conflict of interests.

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