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Central nervous system infections in immunocompromised patients

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ABSTRACT

Diagnosis of CNS infections remains a great challenge in immunocompromised patients with solid cancer or hematological disorders, as it happens with transplant recipients, since symptoms might both be masked and be mimicked by other conditions such as metabolic disturbances or consequences of antineoplastic treatment and the administration of immunosuppressive drugs. Thus, awareness of this complication is crucial and any suspicion of a CNS infection should lead to make an early diagnosis and to choose an appropriate empirical treatment to improve the outcome in this population.

Keywords: Central nervous system (CNS) infection, immunocompromised patient, cancer, hematopoietic cell transplantation, solid organ transplantation.

Infecciones del sistema nervioso central en el huésped inmunodeprimido

RESUMEN

El diagnóstico de las infecciones del SNC en pacientes inmunocomprometidos con cáncer sólido o neoplasias hematológicas, junto a los receptores de trasplantes, sigue siendo todo un desafío clínico. Ello es debido a que la semiología podría ser enmascarada y mimetizada por otras condiciones y factores como las alteraciones metabólicas o ser consecuencia del tratamiento antineoplásico o de la administración de fármacos inmunosupresores. Por ello, el conocimiento de esta complicación es crucial y cualquier sospecha de infección del SNC debería conducir a un diagnóstico adecuado en tiempo y forma y a un tratamiento apropiado con el fin de mejorar el pronóstico evolutivo en esta población de enfermos.

Palabras clave: Infecciones del sistema nervioso central, paciente inmunocomprometido, cáncer, trasplante de progenitores hematopoyéticos, trasplante de órgano sólido.

INTRODUCTION

Infections of the central nervous system (CNS) are infrequently diagnosed in immunocompetent patients, but they do occur in a significant proportion of immunosuppressed and cancer patients, such as patients receiving solid organ transplants (SOT) or with hematological disorders including those with hematopoietic stem cell transplantation (HSCT) [1,2,3].

With improved treatments, patients with many types of cancer survive longer. However, both the acute adverse effects of more intensive therapies and the risks of chronic immunosuppression have led to a diverse and evolving spectrum of CNS infections. The presentation and course of CNS infections in cancer and immunosuppressed patients may be different from those in patients without cancer or with immunocompetent status, complicating and delaying an accurate diagnosis. New syndromes related both to the underlying malignancies and to their treatment, including HSCT in hematological cancer, continue to emerge. Noninfectious disorders such as adverse drug effects, vascular lesions, and radiation effects can mimic CNS infections [4]. The major deficits predisposing patients with cancer to CNS infection are neutropenia, barrier disruption, B-lymphocyte or immunoglobulin deficiency, and impaired T lymphocyte-mediated immunity. Evolving patterns of drug resistance and prophylactic antimicrobial regimens have altered the timing and range of organisms causing infections. Increasingly intensive immunosuppression has made new groups of patients vulnerable to very different and peculiar infections such as progressive multifocal leukoencephalopathy (PML) or limbic encephalitis (LE). New magnetic resonance

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imaging (MRI) sequences offer the potential to diagnose such infections earlier, at a stage when they are more treatable.

Despite improved prophylactic and therapeutic antibiotic regimens, CNS infections remain an important source of morbidity and mortality among several cancer patient groups, particularly those patients undergoing craniotomy and those with hematologic malignancies receiving either HSCT or other intensive chemotherapy regimens. The diagnosis and management of CNS infections in cancer or immunosuppressed patients raises a formidable challenge to neurological consultants. Timely, effective care for these patients requires attention to underlying patient disease and treatment regimen risk factors, prophylactic and vaccination strategies, transfusion safety issues, community and nosocomial epidemiologic trends, travel and zoonotic exposure histories, and changing microbial susceptibilities. Additionally, it is important to recognize that (a) clinical presentations of infections in immunocompromised patients may be atypical or may mimic noninfectious processes, (b) two or more disparate diseases may coexist, and (c) patients can be at risk for infection not only during cancer treatment or transplant procedure, but also before and for an extended period after therapy or transplantation [5].

CNS INFECTIONS IN PATIENTS WITH HEMATOLOGICAL DISORDERS (INCLUDING AUTO- AND ALLOGENEIC STEM-CELL TRANSPLANTATION)

By far, CNS infections are much more frequent and serious in patients with allo-HSCT than in patients with auto-transplant. Patients undergoing allo-HSCT are among those with the highest risk for CNS infections with an overall incidence of up to 15% [6]. Fungi (*Aspergillus* spp.) and *Toxoplasma gondii* are the predominant causative agents. Mucormycosis is diagnosed in ~0.1% of all patients with hematological disorders, but an increased incidence (1.0%-1.9%) has been reported among patients with acute myeloid leukemia (AML). The lungs are frequently infected in mucormycosis, but CNS might be involved in 10%–20% of patients. Among virus, PML is a rare (<1%), but frequently fatal CNS disease caused by the JC virus. It mainly affects allo-HSCT recipients, but also patients after rituximab-based treatment strategies or with multiple lines of immunosuppression. Bacterial CNS infections are rarely diagnosed in patients with hematological disorders, and they occur more frequently in patients with intraventricular devices or after neurosurgical interventions. The diagnosis of CNS infections is based on neuroimaging, cerebrospinal fluid examination and biopsy of suspicious lesions in selected patients. However, identification of CNS infections in immunocompromised patients could represent a major challenge since metabolic disturbances, side-effects of antineoplastic or immunosuppressive drugs and CNS involvement of the underlying hematological disorder may mimic symptoms of a CNS infection [7]. As in the context of SOT recipients, neurologically important syndromes and problematic presentations (table 1) include posterior reversible encephalopathy syndrome (PRES), post-transplantation lymphoproliferative disorder (PTLD) [8] and immune reconstitution inflammatory syndrome (IRIS). The prognosis of CNS infections is generally poor in these patients, despite the introduction of novel substances (e.g. voriconazole, posaconazole, isavuconazole) has improved the outcome in distinct patient subgroups.

CNS infections are a significant clinical problem after HSCT related to poor survival. They were more frequent after umbilical cord blood transplantation (UCBT) compared to HLA-matched sibling donor stem cell transplantation (MST). The incidence, clinical characteristics, prognostic factors, and outcome of CNS infections in consecutive patients receiving UCBT or MST were recently analyzed by a Spanish scientific group [9]. Thirty-four CNS infections were documented at a median time of 116 days after transplantation (range, 7 to 1161). The cumulative incidence (CI) risk of developing a CNS infection was 0.6% at day +30, 2.3% at day +90, and 4.9% at 5 years. The 5-year CI of CNS infection was 8.2% after UCBT and 1.7% after MST ($P < .001$). The causative micro-organisms of CNS infections were fungi (35%), virus (32%), *Toxoplasma* spp. (12%), and bacteria (12%). Fungal infections occurred in 11 patients after UCBT and 1 after MST and were caused predominantly by *Aspergillus* spp. (in 8 cases), followed by *Cryptococcus neoformans* (2 cases), *Scedosporium prolificans* and *Mucor* (one case each). Except for 1 patient, all died from CNS fungal infection. Viral infections occurred in 9 patients after UCBT and 1 after MST and were due to human herpes virus 6, cytomegalovirus, and varicella zoster virus. CNS toxoplasmosis was diagnosed in 3 patients after UCBT and 1 after MST. Other pathogens were *Staphylococcus* spp, *Nocardia* spp, *Streptococcus pneumoniae*, and *Mycobacterium tuberculosis*. Twenty of the 34 patients (59%) died from the CNS infection. UCBT and disease stage beyond first complete remission were independently associated with the risk of developing CNS infections. The 5-year overall survival was 19% in patients who developed a CNS infection and 39% for those who did not.

Some principal aspects regarding the management of CNS infections in patients with hematological disorders should be considered:

(a) The management of CNS infections in patients with hematological disorders requires a high level of awareness, as neurological symptoms could be nonspecific and caused by noninfectious conditions related to the underlying disease and/or side-effects of antineoplastic or immunosuppressive treatment. An additional differential diagnostic consideration to explain a neurological syndrome in a cancer patient with known or suspected CNS infection is a complication of antibiotic therapy itself, as summarized in table 2.

(b) While clinical presentations of CNS infections in immunocompetent hosts are broadly categorized into meningitis, meningoencephalitis, encephalitis, cerebritis/abscess formation and infection of intracerebral devices, diminished inflammatory responses in immunocompromised patients can lead to only subtle symptoms. Mass lesions can be blurred by rather nonspecific cerebral dysfunctions such as confusion or altered consciousness.

Table 1 Differential diagnosis of CNS infection by predominant clinical and MRI Syndrom.

Leukoencephalopathy	Stroke (s)	Limbic encephalitis	Mass lesion (s)	Brainstem
INFECTIONS				
PML-JCV	VZV, CMV*	Herpes simplex types 1 & 2	*Aspergillus* and other molds	*Listeria monocytogenes*
	Emboli (due to endocarditis)	HHV-6	Bacteria (*S. aureus, Nocardia, Bacteroides*)	*Cryptococcus neoformans*
	Vasculitis post-meningitis		*Toxoplasma gondii*	VZV
	Aspergillus, Mucor spp.		EBV associated CNS lymphoma	PML-JCV
NON-INFECTIOUS CONDITIONS				
IRIS, PRES, ADEM	Radiation-related arteriopathy	Hashimoto encephalopathy	IRIS	Wernicke encephalopathy
Pontine / extrapontine osmotic demyelination	Non-bacterial thrombotic endocarditis	Paraneoplastic syndromes (anti-HU, Ma, NMDAR, VGKC)	Secondary tumor (lymphoma, meningioma, astrocytoma, metastases)	Osmotic demyelination
Amphotericin B	CNS vasculitis	Repetitive seizures	Radiation necrosis (pseudoprogression)	PRESS
Valproate				GVHD
Rituximab				Radiation necrosis
Radiation injury				

CNS: Central nervous system; PML-JCV: progressive multifocal leucoencephalopathy (due to JC virus); VZV: varicella-zoster virus; CMV: Cytomegalovirus; HHV-6: Human herpes virus 6; EBV: Epstein-Barr Virus; IRIS: inflammatory reconstitution immune syndrome; PRES: Posterior reversible encephalopathy syndrome; ADEM: Acute disseminated encephalomyelitis. MRI gadolinium enhancement variable for all conditions. *CMV: Variable manifestations (encephalitis, myelitis, polyradiculitis).

Table 2 Neurologic toxicities of antimicrobial agents.

Neurologic Problem	Potential causative agents
Seizures	Penicillin G, imipenem/meropenem, aztreonam, gentamicin, ciprofloxacin, cefepime, ceftazidime, metronidazole, amphotericin B, acyclovir (iv), foscarnet, praziquantel
Potentiation of neuromuscular junction transmission blockade	Aminoglycosides, cephalosporins
Pseudotumor cerebri	Minocycline, tetracycline
Ototoxicity/vestibular	Vancomycin, aminoglycosides, erythromycin, tacrolimus
Delirium	Cefepime, ceftazidime, ciprofloxacin, metronidazole, foscarnet, praziquantel, amphotericin B
Visual hallucinations	Voriconazole
Extrapiramidal signs	Amphotericin B
Headache	Ciprofloxacin, fluconazole, itraconazole, foscarnet, praziquantel, trimethoprim/sulfamethoxazole
Dizziness /cerebellar signs	Metronidazole, aminoglycosides, minocycline, isoniazid, fluconazole, itraconazole, varicella vaccine (ataxia)
Posterior reversible encephalopathy syndrome	Linezolid, roxithromycin
Lymphocytic meningitis	Trimethoprim/sulfamethoxazole, cephalosporins, iv. immunoglobulin, valacyclovir
Tremor	Acyclovir, cephalosporins
Optic neuropathy	Ethambutol, linezolid
Serotonin syndrome	Linezolid (with selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors)

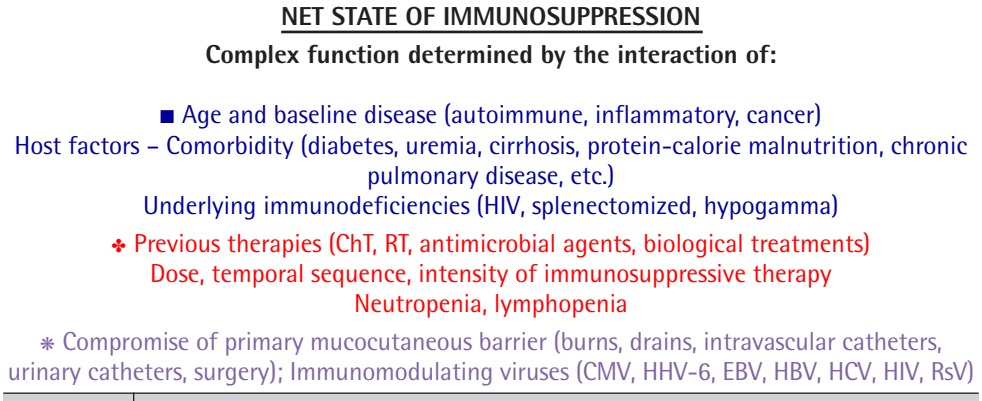

Figure 1 | **Net state of immunosuppression: determining concept of risk of infection.**

ChT: Chemotherapy; RT: Radiotherapy; RsV: Respiratory virus.

(c) Defined patient groups predispose for infections with certain pathogens based on their pattern of immunosuppression (defects in cell-mediated immunity versus defective humoral immunity). Bacterial, fungal and viral CNS infections typically occur in neutropenic patients. Defects in T-cell immunity or in function of macrophages predispose for cerebral toxoplasmosis and cryptococcal meningitis.

(d) Variations in the frequency of causative organisms (e.g. *Toxoplasma* spp. *Histoplasma capsulatum*, *Mycobacterium tuberculosis*) due to regional endemic differences should be taken into account.

Regarding diagnosis, any suspicion of CNS infection should immediately trigger adequate diagnostic procedures including neuroimaging, cerebrospinal fluid (CSF) examination and, in selected cases, biopsy of focal lesions. CSF analyses including various methods such as staining and microscopy, culturing, serological techniques and PCR assays (nowadays with multiplex PCR techniques) are crucial diagnosing meningoencephalitis which is typically caused by viruses, *Candida* spp., bacteria or more rarely by *Cryptococcus* spp. For these CNS infections, brain biopsy is required only in selected cases. Focal lesions, typically caused by *Toxoplasma* or *Aspergillus* spp. are commonly diagnosed by histopathology of suspicious lesions. Histopathological work-up should be done using adequate staining methods such as Calcofluor white. Routine parameters in the CSF are frequently nonspecifically altered in these patients. Neuroimaging should commonly be based on MRI since it is more sensitive than computed tomography (CT) scan for diagnosis of the majority of CNS infections. Further diagnostic methods such as positron emission tomography (PET) might help in selected patients to differentiate infectious from noninfectious CNS lesions.

Given the dismal outcome of delayed treatment in patients with hematological disorders and CNS infection, antimicrobial treatment should be initiated promptly once collection of CSF and blood cultures have been completed. After isolation and in vitro susceptibility testing of a (potentially) causative pathogen, antimicrobial treatment should be modified accordingly. Recommendations for empiric, pre-emptive and targeted treatment are specified and available in several guidelines, articles and consensus documents [10], providing supplementary material to our manuscript. Due to the lack of systematic data, decisions about the duration of antimicrobial treatment should be assessed individually. Treatment strategy (such as antimicrobial drug therapy with or without surgery), resolution of symptoms and recovery of the individual immune-status, as defined by the presence of neutropenia, hypogammaglobulinemia and graft versus-host disease should therefore be taken in account. In patients with persisting complex immunodeficiencies, targeted antimicrobial treatment might be followed by maintenance treatment (e.g. for cerebral toxoplasmosis, cytomegalovirus encephalitis or cryptococcal meningitis). To improve efficacy and minimize toxicity, therapeutic drug monitoring (TDM) might be useful for antimicrobial agents, such as 5-fluorocytosine (5-FC), voriconazole and posaconazole. TDM might be of particular relevance in patients with hematological disorders since impaired gastrointestinal resorption and interferences with concomitant medication are common in this population. Adjunctive treatment may include neurosurgery, platelet transfusion and administration of corticosteroids, anticonvulsants, sedatives or antipyretics.

NEUROLOGICAL COMPLICATIONS DUE TO INFECTION IN SOLID ORGAN TRANSPLANTATION (SOT)

The prevention, diagnosis, and management of infectious disease (including CNS infections) in transplantation are major contributors to improved outcomes in organ transplantation. The risk of serious CNS infections in organ recipients is determined by interactions between the patient's epidemiological exposures and net state of immunosuppression. In organ recipients, there is a significant incidence of drug toxicity and a propensity for drug interactions with immunosuppressive agents used to maintain graft function. Thus, every effort must

be made to establish specific microbiologic diagnoses to optimize therapy. A timeline can be created to develop a differential diagnosis of infection in transplantation based on common patterns of infectious exposures, immunosuppressive management, and antimicrobial prophylaxis. Application of quantitative molecular microbial assays and advanced antimicrobial therapies have improved care. Pathogen-specific immunity, genetic polymorphisms in immune responses, and dynamic interactions between the microbiome and the risk of infection are beginning to be explored.

Approximately one-third (between 10% and 85% according to different series) of SOT patients will experience a neurological complication [11]. While the spectrum of neurological complications varies with the type of organ transplanted, the indication for the procedure, and the intensity of long-term required immunosuppression, major neurological complications occur with all SOT types. Neurological complications common to all SOT not caused by transplanted organ failure are frequently attributable to immunosuppressive regimens. Common neurological complications are seizures, CNS infections, encephalopathy, and stroke. Few neurological complications occur exclusively in a specific transplant population, but both in the early days and throughout their post-transplantation course, recipients of different tissues and organs have predictably varied complication patterns. Among SOT recipients, liver transplant recipients, particularly those with fulminant hepatic failure and coagulopathy, have the most serious medical problems at the time of their transplant with concomitantly more early complications. Months to years after SOT, complication profiles reflect the degree and duration of immunosuppression necessary to prevent rejection. Thus, heart and intestinal/pancreas recipients, the most heavily chronically immunosuppressed groups, are the most prone to late infectious complications.

Those who develop CNS abnormalities will have clinical presentations ranging from generalized encephalopathy or headache to focal neurological deficits. The etiology of these abnormalities is often obscure; symptoms are altered by immunosuppressive therapy. There is an urgency to establish a specific etiological diagnosis to guide therapy. The major categories of "CNS processes" include infection, drug toxicity, anatomic processes (stroke, cancer, vasculitis), and metabolic derangements including those associated with graft dysfunction. These etiologies, infections and non-infectious causes of CNS abnormalities, often coexist in the transplant recipient [12]. For example, post-transplant graft dysfunction (uremia, cardiac, or hepatic insufficiency; hypoxia) can be complicated by infection (sepsis, wound infection, nosocomial pneumonia), drug toxicity (CNS effects of calcineurin inhibitors), stroke, or bleeding. The initial evaluation must identify potentially life-threatening processes. The risk for CNS infection after transplantation rests on two fundamental determinants: Prior exposures and the net state of immunosuppression. The epidemiological exposures of a transplant recipient include those from the hospital environment, from community exposures, from the host as reactivation of latent infections, and from the organ donor. The "net state of immunosuppression" is a concept encompassing patient-specific factors that determine vulnerability to infection (figure 1).

With respect to the timeline of CNS processes, multiple factors contribute to altered mental status and neurological disorders in the post-transplant setting. The intersection of epidemiology and the net state of immunosuppression characterizes the evolving risk for CNS infections. Variability exists with immunosuppressive regimens, antimicrobial prophylaxis, and epidemiology. On these alterations the neurological effects caused by metabolic alterations and drug toxicities are superimposed. This approach creates a timeline for common and more obscure post-transplant CNS syndromes, distributed in a group of successive periods or consecutive phases, which include: Postoperative phase (1–4 weeks), early post-transplant syndromes (1–6 months) and late post-transplant syndromes (6 months and beyond).

CNS infection in the transplant recipient is a medical emergency. A specific diagnosis of CNS processes in transplant recipients is essential for management. The spectrum of causative organisms is broad. Classic signs (headache, meningismus, fever, Kernig and Brudzinski signs, or papilledema) are often absent. Subtle cranial nerve abnormalities may be useful in diagnosis. Neurological signs of infection may be obscured by hepatic encephalopathy, uremia, hypoxemia, drug effects (calcineurin inhibitors, fluoroquinolones, trimethoprim-sulfamethoxazole), systemic infection, or alcohol withdrawal and depression. Empirical therapy has risk for drug toxicities and interactions. Reduced immunosuppression may provoke or exacerbate graft rejection. Immunosuppressed patients with focal neurological deficits require urgent brain imaging. Most transplant recipients with altered mental status also require imaging. CT or MRI studies without contrast (to preserve renal function) may demonstrate mass lesions but lack sensitivity for white matter changes.

Many CNS infections spread from the lungs or sinuses. Thus, "metastatic" evaluations are needed, notably for infections due to fungi (*Aspergillus*, agents of mucormycosis, *Scedosporium* or *Cryptococcus*) [13], bacteria (*Nocardia* spp.) or parasitic diseases (*Strongyloides stercoralis*). Important viral infections include herpes simplex virus meningoencephalitis, cytomegalovirus, JC virus (PML), West Nile virus, and varicella zoster virus. Common bacterial infections include *Listeria monocytogenes*, mycobacteria, *Nocardia* and occasionally *Salmonella* species. Parasites include protozoa and helminths such as *Toxoplasma gondii*, *Microsporidia*, and *Strongyloides*. Specific diagnosis is essential. Empirical therapy must "cover" *Listeria* (ampicillin), *Cryptococcus* (Amphotericin B and/or fluconazole), and herpes simplex virus (acyclovir or ganciclovir), common bacterial pathogens (vancomycin/linezolid, ceftriaxone), and known colonizing organisms while awaiting data from lumbar puncture, blood cultures, and radiographic studies. Included in the differential diagnosis are non-infectious etiologies including calcineurin inhibitor toxicity, PRES, PML, lymphoma (PTLD), and other malignancies. Unique epidemiologic exposures (e.g. Chagas disease, Lyme) must be considered.

Bactericidal or fungicidal agents with CNS penetration are preferred. Broad-spectrum coverage should be maintained until a diagnosis is achieved. The management of immunosuppression must be individualized, such as reducing T-cell suppression in viral infections including EBV-associated PTLD or JC virus–induced PML. Reduced immunosuppression risks immunological rebound with graft rejection, increased inflammation and edema, and/or IRIS manifesting as worsening of CNS symptoms in the face of appropriate therapy and without disease progression. IRIS has been documented in transplant recipients with CMV, tuberculosis, and cryptococcal disease. Acute reductions in corticosteroids during CNS infection, in particular, may provoke hydrocephalus in cryptococcal meningitis or infectious vasculitis or encephalitis flare-ups. CNS PTLD may not respond to reduced immunosuppression; irradiation is often beneficial and CD20+ tumors may respond to monoclonal antibody therapy, although the penetration and activity of rituximab in CNS is insufficient. Immunosuppression must be reinstated when appropriate to avoid graft rejection. Increases in immunosuppression may be helpful, particularly for specific pathogens such as *Streptococcus pneumoniae*. Increased adrenocorticoids may reverse persistent hypotension due to adrenal insufficiency from infection or chronic glucocorticoid use. Some transplant recipients require procedural interventions for management of CNS infection. Cryptococcal meningitis may cause elevated intracranial pressure with hydrocephalus requiring serial lumbar punctures or ventricular shunting. Neurosurgical intervention may be required for acute hydrocephalus due to intraventricular development or rupture of abscesses blocking CSF ventricular flow. Surgical debridement of bacterial abscesses or fungal lesions (e.g., mucorales) may be required for diagnosis and to gain control of progressive, invasive infection [14].

CONCLUSIONS

The diagnosis and management of CNS infections in immunocompromised patients remains challenging and requires constant attention to emerging infections, prophylactic strategies, transfusion safety issues, epidemiologic trends, travel histories, changing microbial susceptibilities, synergistic infections, and evolving cancer regimens or anti-rejection drugs that will continue to impact the nervous system. Finally, the effective consultant should never discount the possibility that two or more disparate diseases (neoplastic, infectious and autoimmune) may exist concurrently. Despite efforts to stratify patients by risk factors, clinical syndromes, and appropriate diagnostic studies, diagnostic and therapeutic dilemmas are common and outcomes remain, despite the *neuroinfectologist's* best efforts, frequently disappointing.

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