REVIEW ARTICLE (PREGLEDNI RAD)

Radiological Management of Infections in Immunocompromised Patients

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Summary

Immunocompromised status is defined as a condition of impaired or dysfunctional immune system, which is unable to protect the body from external pathogens. The causes of immunocompromised status can be congenital or acquired, with the most notable example worldwide being the human immunodeficiency virus. An immunocompromised patient has an increased susceptibility to infections, which can be caused by pathogens such as fungi, parasites, bacteria, or viruses.

The use of appropriate radiological methods in diagnostic purpose plays an important role in the early detection and treatment of various infections and other diseases characteristic for immunocompromised patients.

Immunocompromised patients most commonly develop opportunistic infections of the neurological system. Since neurological changes in the early stages of development can be undetectable on CT scans, magnetic resonance imaging is primarily used for promt disease detection, as it is the most specific and sensitive method for these conditions. During MRI imaging, it is crucial to use multiple different pre-contrast and additional post-contrast sequences to reliably confirm highly specific neurological infections and differentiate them based on the type of etiological factor. Besides neurological complications, immunocompromised patients are also highly prone to developing respiratory infections. The method of choice for such complications is undoubtedly multislice CT, which can detect even the smallest changes within the respiratory system in the early stages of the disease. After the initial detection of the disease, radiographic imaging of the thoracic region represents an extremely powerful and accessible tool for further monitoring, with significant sensitivity that can guide the subsequent course of treatment.

Key words: HIV; immunodeficiency, infections, radiology

Abbreviations and acronyms: ADC (Apparent Diffusion Coefficient), AIDS (Acquired Immunodeficiency Syndrome), CE-T1 WI (Contrast-Enhanced T1-Weighted Imaging), CNS (Central Nervous System), CMV (Cytomegalovirus), CSF (Cerebrospinal Fluid), CT (Computed Tomography), DWI (Diffusion-Weighted Imaging), FLAIR (Fluid Attenuated Inversion Recovery), HAND (HIV-Associated Neurocognitive Disorders), HIV (Human Immunodeficiency Virus), HRCT (High-Resolution Computed Tomography), HSV (Herpes Simplex Virus), MRI (Magnetic Resonance Imaging), NK (Natural Killer), PCNSL (Primary Central Nervous System Lymphoma), PID (Primary Immunodeficiency Disease), PJP (Pneumocystis Jiroveci Pneumonia), SCID (Severe Combined Immunodeficiency), SPECT (Single Photon Emission Computed Tomography), SWI (Susceptibility Weighted Imaging), T1 WI (T1-Weighted Imaging), T2 WI (T2-Weighted Imaging)

Introduction

Immunocompromised patients may have a compromised immune system due to acquired (primary) factors, iatrogenic factors or hereditary factors. Causes of immunodeficiency can be infectious, such as the human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS). Also, there are solid organ or bone marrow transplants, cancer, chemotherapy, radiotherapy, lymphoma, glucocorticoid therapy, splenectomy, and traumatic injuries. Immunocompromised patients are at an increased risk of life-threatening infections, which must be treated as early as possible in their development (1).

Congenital forms of immunodeficiency are often associated with acquired immunodeficiency syndrome (AIDS), caused by the HIV. Malignant diseases, particularly hematopoietic and lymphoid cancers, lead to immune dysfunction by causing a deficiency in immune effector cells or dysfunction in antibody synthesis. Additionally, the use of cytostatics in chemotherapy, as well as radiotherapy used in the treatment of cancer patients, has a negative impact on the immune system, leading to a state of immunodeficiency (2).

The risk of infection in immunocompromised patients can be classified as high, moderate, or low, depending on the cause of the immunodeficiency. Infections in these patients can be caused by a variety range of pathogens, which are generally divided into fungal, parasitic, bacterial, and viral pathogens.

Aim of the paper

The aim of the paper is to provide a detailed explanation of the types of immunocompromised conditions and the opportunistic infections that may develop. The role of radiology in diagnosis, treatment, and monitoring of such patients is defined. Each relevant radiological method in diagnosis of these conditions is explained and further supported with illustrative examples. The article was written using available articles from the PubMed platform, as well as professional books in both physical and digital formats. When searching the literature on the internet, the terms *radiology, infectology, immunodeficiency,* and *immunocompromised* were used, with the operators *AND* or *OR*. All results found online were presented in a narrative and descriptive form in English, and each article or paper was publicly available in its entirety.

Discussion

1. Immunocompromised host

Immunocompromised state, immunodeficiency, or immunosuppression are synonymous terms that describe a condition of impaired immune function and an increased risk of infections. This condition can manifest due to a congenital or acquired disorder affecting one or more immune components of the the organism. It most commonly refers to patients with some form of congenital immune deficiency, such as primary immunodeficiency, as well as those who have become immunocompromised to other conditions, including individuals infected with the HIV. Acquired immunocompromised states may result from malignant diseases or can be iatrogenic, meaning they occur as a consequence of certain treatments, such as cytostatic therapy, organ transplantation, splenectomy, chemotherapy, or radiotherapy (3).

1.1. Causes of immunosuppression in patients

Primary immunodeficiency disease (PID) refers to a highly diverse group of disorders characterized by severely weakened or absent immune system function, either fully or partially. Such immunological impairments in individuals lead to an increased risk of developing severe infections, autoimmune diseases, or malignant conditions. Patients with specific T-cell defects may have abnormally low levels of lymphocytes and neutrophils, known as lymphopenia and neutropenia. In the most severe forms of severe combined immunodeficiency (SCID), T-cell deficiency is frequently observed, often accompanied by a corresponding B-cell deficiency (4). Antibody deficiency, or B-cell dysfunction, is the most common type of immunodeficiency, accounting for 50% of all PID cases (5).

Solid Organ Transplantation is the definitive therapy for many severe organ diseases that can no longer be effectively treated by medication or surgery. However, the transplanted organ (allograft) triggers an immune response from the recipient, which, without adequate systemic immunosuppression, would lead to allograft rejection, then procedure failure, and potentially fatal outcomes. While immunosuppression has significantly improved graft survival, it also left patients more susceptible to pathogens and infectious complications. Glucocorticoids were the first agents used for immunosuppression in solid organ transplantation. They are considered highly potent but non-selective, affecting multiple cell types, including T and B cells, macrophages, granulocytes, and monocytes, leading to systemic immunosuppression (6).

Advancements in radiotherapy techniques have led to increased precision in dose delivery and better protection of surrounding healthy tissue. However, radiotherapy treatments not only affect adjacent tissues but also have systemic adverse effects. The most pronounced harmful effects of ionizing radiation occur in the tumor microenvironment. In general, lymphocytic cells, particularly B cells and natural killer (NK) cells, are among the most radiosensitive cells in the body. Their destruction directly correlates with immune system weakening. The effects of radiation on the tumor microenvironment and the overall immune system can be modulated by fractionating of radiation doses. Numerous studies have reached a universal conclusion: the use of hypofractionated high doses instead of high single doses significantly reduces the immunosuppressive effects of radiation on healthy tissue (7).

2. Human immunodeficiency virus (HIV)

The human immunodeficiency virus belongs to the family of human retroviruses. The virus first emerged in 1981 when it was described as an unexplained pneumonia affecting several homosexual patients. By 1983, the virus had been discovered, when a group of French scientists successfully isolated it. And the following year, it was confirmed that HIV is the main and only cause of AIDS (8).

Over the years, HIV has remained one of the major global health challenges. More than 40 million people worldwide are currently infected with some subtype of the virus. Some countries even reporting an increase in the number of cases (9). The virus is transmitted through three primary routes: sexual contact, blood exposure, and maternal-fetal transmission.

There are two main types of HIV: HIV-1, the dominant and more easily transmissible form, it is responsible for the global pandemic (Figure 1). The second one is HIV-2, which is mostly localized in West and Central Africa, has lower virulence. HIV treatment is highly challenging due to the virus's constant mutation. As the immune response and antiretroviral drugs exert pressure on the virus, its population within the body continuously evolves. This means that the initial virus, which was responsible for the infection can completely change within just a few days (3).

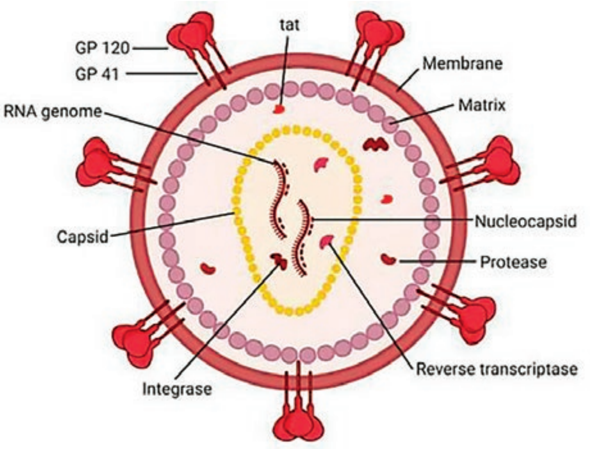

Figure 1. Illustration of human immunodeficiency virus (HIV-1).
Source: https://pubmed.ncbi.nlm.nih.gov/33572761/

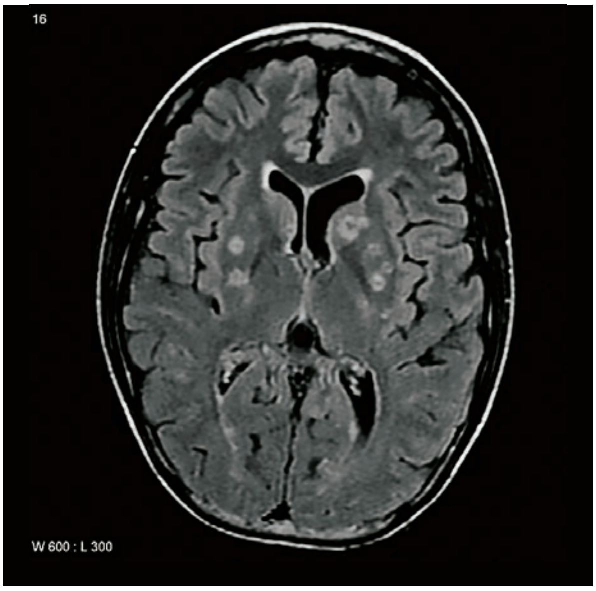

Figure 2. MRI, axial image of brain in FLAIR sequence, ring-enhancing lesions caused by toxoplasmosis infection (HIV patient).
Source: https://radiopaedia.org/articles/toxoplasmosis-vs-lymphoma

2.1. Imunopathogenesis

During the first week of infection, the virus remains undetectable but is highly destructive, leading to the irreversible loss of 80% of the total T helper cells in organism. The virus infects monocytes/macrophages as well as active $CD4^+$ cells and also T lymphocytes, which are in adults predominantly located in the lymph nodes (3).

Once the virus enters the bloodstream, it initially spreads to the spleen and other lymphoid organs**,** where the primary infection begins. After a certain period, HIV establishes itself in lymphoid organs and disseminates into various organ systems, including the central nervous system, where it is protected from the systemic immune response. The virus evades both cellular and humoral immunity, not immediately killing its host but instead actively replicating and progressing toward chronic infection. Persistent viremia also depletes B lymphocytes, leading to weakened humoral immunity (3).

In untreated patients, approximately 10 years after the initial infection**,** HIV disease progresses to an advanced stage. The $CD4^+$ cells count is critically low, leading to significant immunosuppression, making individuals highly susceptible to opportunistic infections and malignancies. Thanks to antiretroviral therapy, even patients in advanced stages of the disease can live long lives with HIV (3).

2.2. Neuroimaging of HIV-associated disorders

Neurological manifestations caused by the human immunodeficiency virus are very common. Around 20% of HIV-infected patients notice their first symptoms through neurological abnormalities, while 30-40% of patients in the advanced stage of HIV infection develop some form of neurological impairment. The term HIV-associated neurocognitive disorders (HAND) is used to describe a spectrum of various asymptomatic disorders that can only be detected through neuropsychiatric testing. It is estimated that around 50% of infected patients (even those receiving antiretroviral therapy) exhibit some form of HAND (3).

Among opportunistic diseases associated with HIV infection, cerebral toxoplasmosis is very common. It presents with ring-enhancing lesions in the basal ganglia region or at the corticomedullary junction (the boundary between gray and white matter), often surrounded by significant edema (Figure 2) (3).

Another frequently observed condition is primary central nervous system lymphoma (PCNSL), which appears on CT and MRI scans as a periventricular lesion with irregular contrast enhancement (Figure 3). In addition to diagnostic radiology, lymphoma patients are often examined using nuclear medicine imaging techniques, such as single-photon emission computed tomography (SPECT). This method utilizes thallium-201 to analyze its accumulation in the brain, reflecting increased metabolic activity (3,4).

Figure 3. MRI, axial image of brain in T2 sequence, brain lymphoma caused by HIV infection.
Source: https://radiopaedia.org/articles/toxoplasmosis-vs-lymphoma

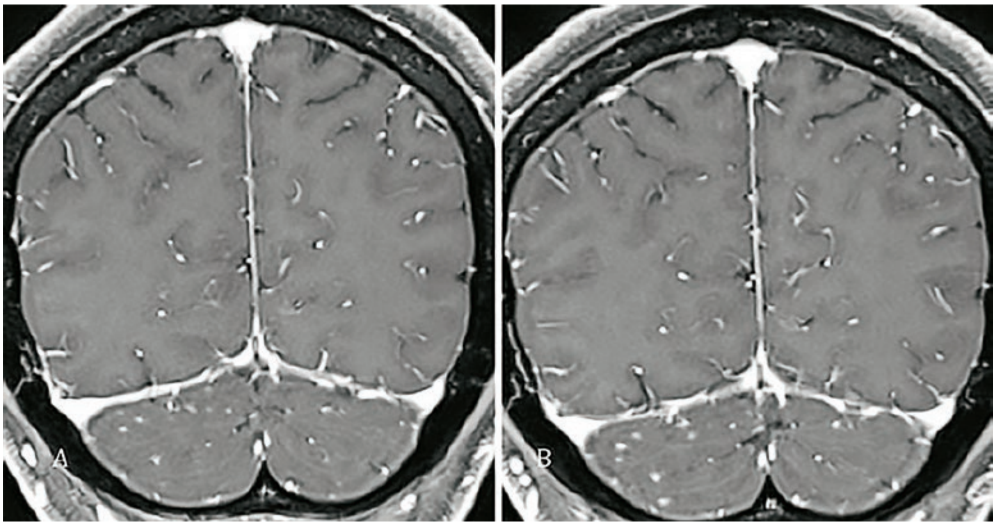

Figure 4. MRI, coronal contrast-enhanced brain images, show nodular leptomeningeal enhancement in the posterior fossa in the HIV patient with cryptococcus meningitis.
Source: https://link.springer.com/referenceworkentry/10.1007/978-3-319-61423-6_48-1

3. The radiological diagnosis of infetcions

3.1. Fungal infections

Fungi are widespread organisms, but only a few species are actually pathogenic and capable of causing pathological disorders in the body. Several different types of fungal forms are distinguished based on their morphological structure. Fungi represent a significant medical problem in patients with various forms of immunosuppression, as they cause invasive infections that are a frequent cause of mortality in such patients. It is estimated that more than 80% of patients with fungal infections are fundamentally immunocompromised (10).

3.1.1. Cryptococcosis

Meningitis caused by Cryptococcus occurs as a secondary reaction to the spread of the Cryptococcus fungus into the meningeal microcirculation. It is considered as the most common fungal infection of the central nervous system (CNS) (10,11). Magnetic resonance imaging is the method of choice for visualizing pathological changes affecting the meninges. FLAIR (Fluid Attenuated Inversion Recovery) sequences show high signal intensity of the the subarachnoid spaces, which is also confirmed by contrast-enhanced T1-weighted imaging (CE-T1 WI), highlighting the leptomeningeal space. Post-contrast enhancement can appear smooth or thick, nodular and irregular, long and coninuous or asymmetric (Figure 4). FLAIR contrast sequences are often used for detecting pathological changes, and in cryptococcosis, ventricular space dilation is frequently observed (10).

Meningitis caused by cryptococcosis also leads to the formation of pseudocysts outside the Virchow-Robin space, which appear on MRI scans as asymmetrical cystic lesions with a "soap-bubble" appearance. These lesions have the same intensity as cerebrospinal fluid (CSF) and do not show diffusion restriction on diffusion-weighted imaging (DWI) sequences (10).

3.1.2. Aspergillosis

Aspergillosis often presents with multiple abscesses located near the gray-white matter junction, but they can also appear in the deep gray matter nuclei, which is not typically the case with abscesses caused by bacterial infections. On T2-weighted MRI scans, these abscesses most commonly present as a centrally localized hypointense signal surrounded by hyperintense perifocal edema. On contrast-enhanced T1-weighted images, fungal abscesses appear with a thin ring-shaped capsule that also has an irregular outer margin (Figure 5). On T2-weighted sequences, a hypointense signal zone with a thin contrast-enhancing rim can be differentiated, which is significantly thicker than the contrast rim seen on post-contrast T1-weighted images (10).

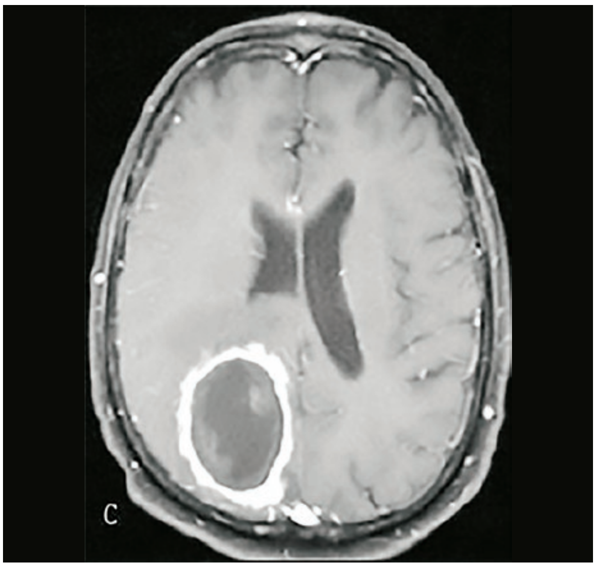

Figure 5. CE-T1 WI, abscess with peripheral contrast enchancment.
Source: https://link.springer.com/referenceworkentry/10.1007/978-3-319-61423-6_48-1

The DWI sequence is crucial for differentiating fungal abscesses from bacterial ones. Both bacterial and fungal abscesses in the brain show diffusion restriction within the abscess cavity, but unlike bacterial abscesses, fungal abscesses exhibit an inhomogeneous signal within the cavity on DWI sequences. The SWI (Susceptibility-Weighted Imaging) sequence is also used to differentiate fungal infections from bacterial infections. On SWI sequences, fungal abscesses manifest with a thick, single, dark rim, and in immunocompromised hosts, multiple dark areas within the abscess cavity are frequently observed (10).

Aspergillosis can also develop within the respiratory system and may exhibit a highly invasive nature. In the semi-invasive type of aspergillosis, CT scans of the thoracic region highlight unilateral or bilateral segmental areas of consolidations. In the angioinvasive type of aspergillosis, the most common manifestation is the Halo sign, which represents multiple nodules surrounded by a ground-glass opacities in the lung parenchyma. Additionally, this type of aspergillosis may present with consolidations and even hemorrhagic infarctions (14).

3.1.3. Candidiasis

Candida albicans is one of the most common fungal infections and is particularly prevalent in immunocompromised patients. Candida has the ability to transform into hyphal forms, which leads to a significantly more invasive parenchymal disease. It most commonly manifests as multiple small brain abscesses (<3 mm) or exhibits angioinvasive behavior, causing thrombosis or hemorrhages (11).

Cerebral microabscesses caused by Candida sometimes can be very small and may not be visible on CT brain scans. Therefore, MRI is the preferred method for detecting these small abscesses. These abscesses are typically seen as small ring-enhancing lesions at the gray-white matter junction and in the basal ganglia. On FLAIR images, areas of hypointense signal are observed in parenchymal regions affected by Candida abscesses. On T2-weighted images, these areas appear ring-shaped with a higher signal intensity. In SWI sequences, the abscesses present with a dark peripheral rim. The DWI sequence is particularly useful for early disease detection, as post-contrast T1-weighted images may initially show no abnormalities. On DWI, Candida abscesses appear as multiple punctate zones of restricted diffusion, bilaterally localized in the basal ganglia and cerebral cortex (Figure 6) (10).

3.1.4. Pneumocystis jiroveci pneumonia (PJP)

In immunocompromised patients infected with the fungus Pneumocystis jirovecii, abnormalities develop within the respiratory system. In these patients, chest radiography can differentiate various pathological changes in more than 90% of cases. Typical findings include bilateral inflammatory processes, usually diffusely distributed, with a predominant perihilar localization (14).

On CT scans, a characteristic ground-glass opacity is observed, along with interlobular septal thickening (14). The absence of ground-glass opacity on CT imaging can, with high probability, exclude Pneumocystis jirovecii as major cause of described pneumonia (3). Additionally, it is important to emphasize that clinical experience has shown that in immunosuppressed patients, particularly those HIV-positive, Pneumocystis jirovecii pneumonia (PJP) is a very common comorbid diagnosis (14).

3.2. Parasitic infections

Various pathogenic species, when and if they colonize a host organism, can establish different types of relationships with it: mutualistic, symbiotic, or parasitic. The parasitic relationship is the most detrimental to the host, as the colonizing pathogen benefits at the host's expense. Although, in theory, every infectious pathogen can be considered as a type of parasite due to its relationship with the host, only certain eukaryotic subtypes (which do not belong to viruses, bacteria, or fungi) have been classified specifically as parasites.

3.2.1. Toxoplasmosis

Toxoplasmosis is a condition caused by the parasite Toxoplasma gondii, which is considered the most common opportunistic infection of the central nervous system in patients with AIDS. Once it enters the human body, T. gondii settles in the brain, retina, striated muscles, and cardiac muscle. If the infected individual has a functional immune system, the parasite remains in a dormant state. However, in immunocompromised individuals, T. gondii begins to proliferate. Initially, the infected person may

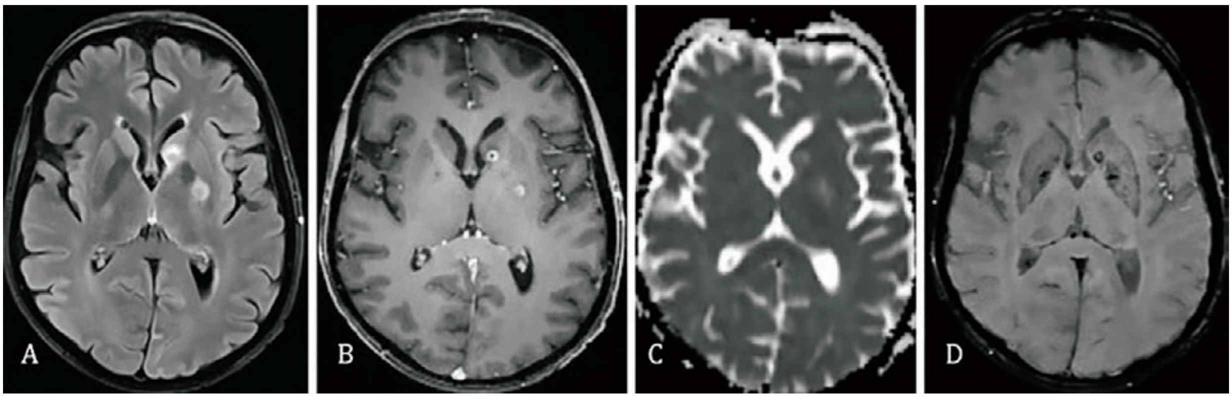

Figure 6. Microabscesses caused by Candida on MRI FLAIR, T2 weighted, DWI and SWI images.
Source: https://link.springer.com/referenceworkentry/10.1007/978-3-319-61423-6_48-1

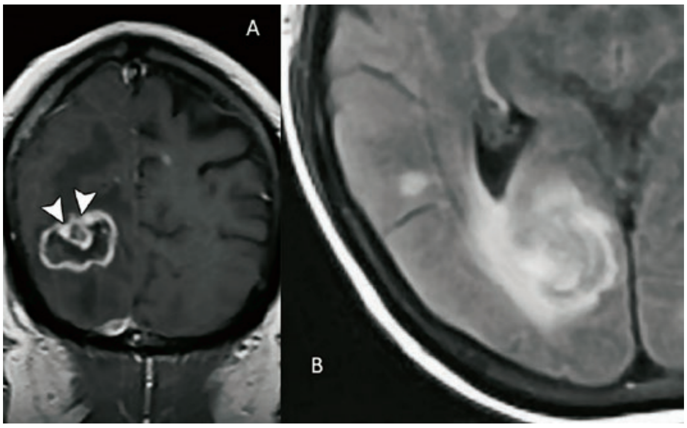

Figure 7. Image A displays brain MRI, coronal view, CE-T1 WI, „eccentric target sign“. Image B displays brain MRI, axial view, FLAIR, „concentric target sign“. *Source:* https://link.springer.com/referenceworkentry/10.1007/978-3-319-61423-6_48-1

experience symptoms such as seizures, microcephaly, fever, and lymphadenopathy. Once the central nervous system is affected, symptoms such as headaches, convulsion and others follow (11).

Neuroradiological imaging of patients with toxoplasmosis reveals multiple abscesses in the basal ganglia, cortex, thalamus and cerebellum (10). The vast majority of lesions identified through CT scans exhibit a ring-like pattern with a surrounding zone of perifocal edema (13). Lesions can be further differentiated using MRI with a contrast-enhanced T1 weighted sequence, which highlights peripheral enhancement of the lesion that may appear nodular, ring-shaped, or irregular (10).

There are two characteristic imaging patterns that distinguish toxoplasmosis lesions from others causes. The first is the „eccentric target sign“, which presents as a ring-like zone of a peripheral contrast-enhancment with small eccentic nodule along the wall (Figure 7). Although considered highly indicative of toxoplasmosis, it is observed in only about 30% of cases. The second common pattern is the “concentric target sign” on T2-weighted MRI images, which shows alternating concentric layers of hypo- and hyperintensity (Figure 7) (10).

3.2.2. Echinococcosis

The disease caused by the Echinococcus parasite manifests in two common forms in the human body. Cystic echinococcosis (hydatid disease) is caused by Echinococcus granulosus, a canine tapeworm that is most commonly transmitted via the fecal-oral route (11). The second type, alveolar echinococcosis, is a much more severe and dangerous condition. It is caused by Echinococcus multilocularis, with foxes being the primary carriers. This tapeworm primarily affects the liver, while brain and lung involvement is extremely rare. The advanced stage of alveolar echinococcosis is characterized by intrahepatic lesions that infiltrate the vascular structures of the liver, ususally extend to the diaphragm, and may spread even further (14).

Radiological diagnosis of intrahepatic lesions is relatively straightforward due to their characteristic appearance. On a X-ray image of abdominal region, ring-like hepatic calcifications may be observed, suggesting the presence of such a lesion. For confirmation, additional imaging such as ultrasound and CT scan can be performed (15).

3.2.3. Malaria

Malaria is considered the most significant parasitic disease worldwide, primarily due to its high incidence, with 300–500 million new cases each year, and an estimated 2 million deaths annually (11). It is transmitted by the Anopheles mosquito and caused by the Plasmodium parasite. With timely treatment, malaria can be effectively managed and symptoms resolve quickly. However, in untreated patients, severe complications may arise, including cerebral malaria, anemia, and ultimately death (16).

On MRI scans, cerebral malaria may present as diffuse brain edema caused by micro-occlusions. DWI sequences reveal cortical infarcts and there is non-specific hyperintense signals on T2 weighted images, along with hemorrhagic infarcts in the corticomedullary junction and deep white matter. Additionally, there have been detailed reports of cases showing hyperintense signals in T2 and FLAIR sequences, localized in the splenium of the corpus callosum, accompanied by diffusion restriction on DWI sequences and ADC maps, though without contrast enhancement of the described lesion (Figure 8) (11).

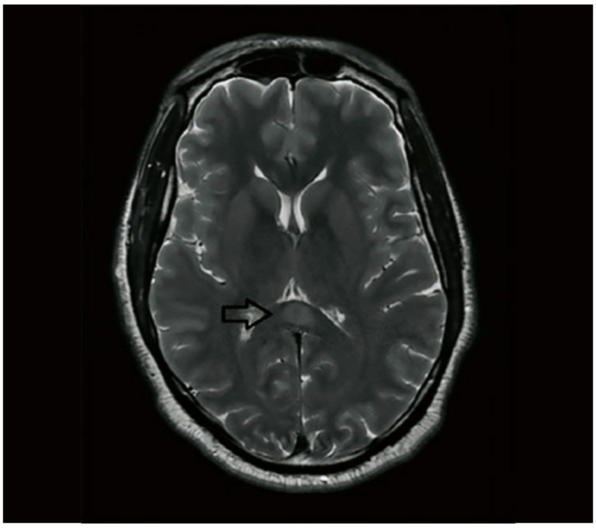

Figure 8. MRI, T2 WI, axial view of brain, display of hyperintense signal localized in the splenium of the corpus callosum.
Source: https://radiopaedia.org/cases/cerebral-malaria

3.3. Bacterial infections

3.3.1. Pyogenic meningitis

Meningitis is an inflammatory condition of the meninges that includes inflammatory processes divided into two categories: leptomeningeal (pia mater and arachnoid) and pachymeningeal (dura mater). The most common causes of pyogenic meningitis are Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae. It most commonly develops in patients with chronic illnesses and immunocompromised individuals (17).

Computed tomography is frequently used in the early stages of the disease, primarily as a native CT scan of the head, performed before a lumbar puncture to rule out the presence of pathological changes causing increased intracranial pressure, which would ultimately be a contraindication for lumbar puncture. Occasionally, during such CT examinations, mild hyperdense reductions in the subarachnoid spaces may be observed as incidental findings. These changes represent a typical sign of pyogenic meningitis but are very difficult to detect, often leading to false-negative results (11).

During MRI scans, at some patients diagnosed with pyogenic meningitis, images may show abnormal hyperintensities within the cerebral sulci on T2, FLAIR, and diffusion-weighted sequences (Figure 9). Another very common sign is an abnormal increase in signal intensity in the pia mater and subarachnoid space. A thin linear hyperintense signal in the cerebral sulci is highly characteristic of acute bacterial meningitis. Additional MRI sequences that can be used to confirm leptomeningeal disease include post-contrast FLAIR and delayed post-contrast T1 weighted sequences. (11)

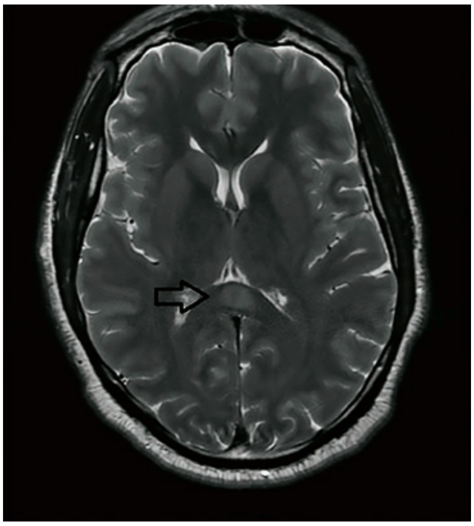

Figure 9. Brain MRI, axial view, FLAIR sequence, display of hyperintense signal distributed diffusely within cerebral sulci. *Source:* https://radiopaedia.org/cases/bacterial-meningitis-1

3.3.2. Pyogenic spondilitis

Infections affecting the spinal cord often originate from the vertebral bodies, which are richly supplied with blood, and then spread through the intervertebral discs to the medulla. The most commonly affected region is the lumbosacral spine, followed by the thoracic and cervical regions. These infections are most frequently caused by the bacterium Staphylococcus aureus (55–90%), followed by Streptococcus, Pneumococcus, Enterococcus, E. coli, and others (18).

During the inflammatory process, spondylitis typically involves two vertebrae, the intervertebral disc, and part of the spinal cord, which is why this condition is often referred to as spondylodiscitis. On T1-weighted MRI sequences, the affected vertebrae appear as hypointense signals with an unclear distinction between the two affected vertebrae (Figure 10). The same area on T2-weighted images shows a high-intensity signal (Figure 10). The affected disc exhibits a signal similar to fluid on both T1- and T2-weighted images. After application of gadolinium-based contrast medium, the infected disc enhances with it. This enhancement can be homogeneous throughout the disc, partially affecting the disc or be present as thicker or thinner peripheral linear zones. The bone marrow within the infected vertebra also enhances with contrast, which is best visualized on fat-saturated sequences. The spread of infection into the paravertebral or epidural spaces may present as an abscess, which appears isointense or hypointense compared to the medulla on T1-weighted images and hyperintense on T2-weighted images (18).

3.3.3. Bacterially caused respiratory infections

The most prevalent bacterial cause of community-acquired infections is Streptococcus pneumoniae. It typically manifests as lobular pneumonia and often leads to bilateral consolidations. Staphylococcus aureus is a notable pathogen frequently found in hospital-acquired infections. Radiographic findings often reveal a bronchopneumonia pattern, while CT scans provide a more detailed depiction of centrilobular nodules with bronchial wall thickening (23). Nocardiosis, a Gram-positive bacterial infection, primarily affects immunocompromised patients, especially those who have undergone solid organ transplantation (most commonly lung transplants). Though rare, the infection has an extremely high mortality rate of up to 80% (12). Radiographic imaging of nocardiosis typically shows multiple consolidations as a reaction to abscess formation. In chronic cases, pleural thickening, bronchospasm, and fluid collections may be present (23).

3.4. Viral infections

3.4.1. Infections caused by cytomegalovirus (CMV)

Cytomegalovirus (CMV) is a DNA virus belonging to the herpesvirus family. Once it enters the human body, it remains dormant until the host enters an immunosuppressive state, triggering its reactivation (10). CMV most commonly manifests as infections of the neurological and respiratory systems.

CMV-induced encephalitis almost exclusively occurs in severely immunocompromised patients. On MRI scans, there are presentation of cortical atrophy and hyperintensities of white matter localized diffusely on T2 and FLAIR sequences (Figure 11). If periventricular or subependymal signal enhancement is noted in immunocompromised patients, CMV infection or the presence of lymphoma should be suspected. Additionally, solitary brain masses are very rare. It is important to note that MRI alone cannot confirm or exclude CMV infection, and because of that lumbar puncture and analysis of cerebrospinal fluid are necessary for definitive diagnosis (10).

More than 50% of virally induced pneumonias in immunocompromised patients are caused by CMV, making

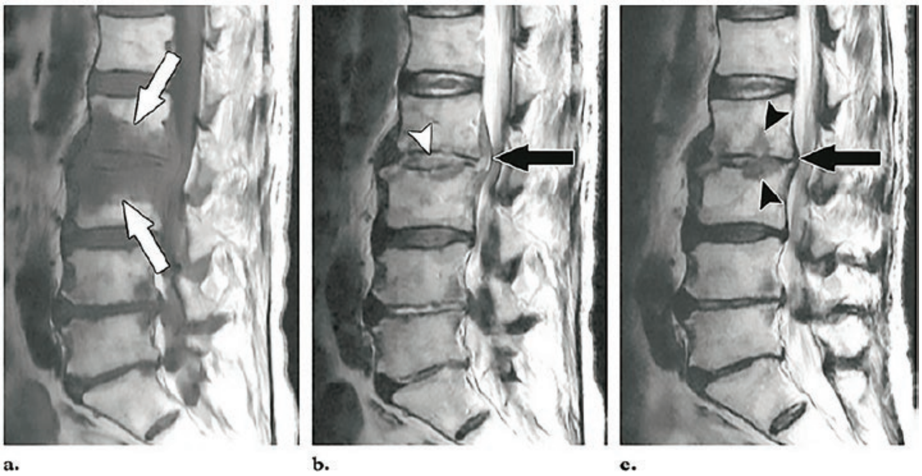

Figure 10. Image A displays MRI T1 WI, sagittal view; arrows indicate a hypointense signal in the vertebral bodies of L2 and L3, along with the corresponding disc. Image B displays MRI T2 WI, showing increased signal intensity in the affected disc, accompanied by an epidural abscess. Image C displays MRI T2 WI, taken two months after image B, demonstrating a reduction of the abscess, but progression of vertebral erosion.
Source: https://pubmed.ncbi.nlm.nih.gov/19325068/

it one of the most prevalent pathogens. On radiographic images, CMV pneumonia typically presents as unilateral or bilateral interstitial infiltrates, alveolar consolidations, and a ground-glass opacities. Some radiological signs of CMV infection may overlap with those of Pneumocystis jirovecii pneumonia; however, pleural effusions are more common in CMV pneumonia (12). CT imaging reveals consolidations, a ground-glass opacities, and centrilobular nodules. Additionally, in HIV-positive patients, discrete pulmonary masses ranging from 1 to 3 cm in size may also be present (23).

3.4.2. Infections caused by herpes simplex virus (HSV)

The herpes simplex virus is divided into two types: the first type is HSV-1, which causes encephalitis in older children and adults and is one of the most common causes of sporadic encephalitis worldwide. The second type, HSV-2, primarily causes encephalitis in neonates and immunocompromised hosts (20).

CT imaging is often the first method used for disease detection, helping to confirm or rule out conditions such as hemorrhage or increased intracranial pressure. Due to its lower sensitivity, CT frequently produces false-negative results in the early stages of the disease. It takes 3 to 4 days for the first abnormalities to be seen on CT images in the temporal or frontal lobes. The abnormalities commonly include areas of hypodensity, hemorrhage, or edema. Contrast changes may not be visible until a week after onset (20).

Unlike CT, MRI is significantly more sensitive in detecting encephalitic changes caused by the herpes simplex virus. The presence of brain lesions manifests as hypointense signals on T1-weighted sequences and hyperintense signals on T2-weighted and FLAIR sequences. Initial abnormalities appear as changes in white matter, primarily localized in the temporal lobe before spreading frontally (Figure 12). FLAIR sequences show thalamic involvement, which is not evident on DWI sequences. Contrast-enhanced T1 sequences often do not show changes in the early stages of the disease, but in advanced stages, there is an increased signal in the gyri, leptomeningeally, or diffusely throughout the brain (21). In immunocompromised patients, the affected area of cerebrum is larger and may include the medulla oblongata and cerebellum (20).

3.4.3. Infections caused by influenza A virus (H1N1)

An immunocompromised host has a very high tendency to get infected with influenza A virus, and the resulting symptoms are significantly more severe, with an increased possibility of complications compared to individuals with a stable immune system. The most common complication in immunocompromised patients infected with influenza A virus is pneumonia, while neurological complications

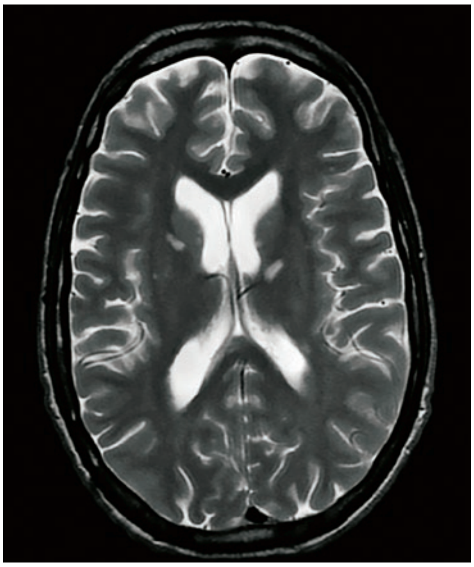

Figure 11. MRI of brain, axial view in T2 WI. Display of multiple periventricular areas of hyperintense signal at patient with CMV infection.
Source: https://radiopaedia.org/cases/cmv-ventriculitis-and-encephalitis

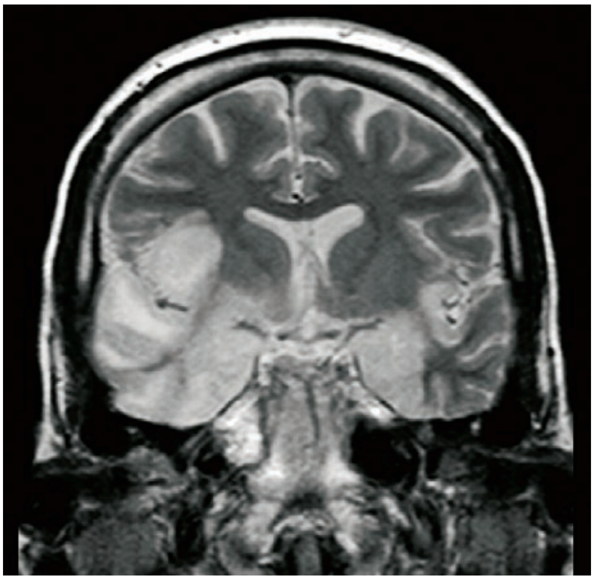

Figure 12. MRI of brain, coronal view in T2 WI. Display of hyperintense signal in the temporal lobes, extending to the hippocampus and the lower right frontal gyrus. *Source:* https://radiopaedia.org/cases/hsv-encephalitis-2

are rarer and include epilepsy, encephalitis, meningitis, and Guillain-Barré syndrome. In addition to these, other inflammatory conditions affecting different organs may also occur. In immunocompromised patients, influenza A often develops as a co-infection with bacterial and fungal pathogens (22).

Influenza A virus most commonly presents with abnormalities in the lower respiratory tract. In a study by Amorim et al., which retrospectively analyzed 71 patients with H1N1 infection in 2009, high-resolution computed tomography (HRCT) findings of respiratory changes were presented. According to the study, the most frequently detected finding was a ground-glass opacities, followed by consolidations, which often appeared in combination. Additionally, bronchial wall thickening, interlobular septal thickening, and a crazy-paving pattern were relatively common. Pleural effusion was rarely observed, and when present, it was minimal (Table 1) (23).

Table 1. Distribution of HRCT findings in 71 patients with influenza A virus. (23).

Finding	Frequency	
	No of patients	Percentage (%)
Ground-glass opacities	60	85
Consolidations	46	64
Airspace nodules	18	25
Bronchial wall thickening	18	25
Interlobular septal thickening	15	21
Crazy-paving pattern	11	15
Perilobular pattern	2	3
Air trapping	2	3

Conclusion

Radiological imaging methods are a essential tools for establishing an accurate diagnosis, which leads to the prompt initiation of patient treatment. This is particulary crucial for immunocompromised patients, where time is a decisive factor in implementing an appropriate therapeutic approach.

Since immunocompromised patients are exposed to a wide range of aggressive pathogens that can cause highly specific infectious changes, it is essential to select their diagnosis method appropriately. For detecting infectious changes within the neurological system, MRI has proven to be an exceptionally reliable method. In addition to standard T1 WI and T2 WI sequences, DWI sequence should also be performed to clearly differentiate etiological factors and identify the causative pathogen. Alongside these pre-contrast sequences, post-contrast T1 and FLAIR sequences should also be conducted to determine the localization and extent of any inflammatory processes within the cerebrum, medulla oblongata or cerebellum. When diagnosing spondylitis or spondylodiscitis, fat-saturated sequences additionally highlight inflammatory processes within the discs and vertebrae.

Fungal and viral pathogens that cause infectious changes within the respiratory system can be reliably detected through HRCT, due to its extremely high sensitivity and specificity. Once the diagnosis is successfully established and the extent of inflammatory processes within the system is determined, follow-up diagnostics at shorter intervals can be conducted using a standard chest X-ray.

Radiology provides a comprehensive imaging overview of all infectious conditions that develop within the human body. Depending on the type of pathogen and the disease's localization, radiology offers an appropriate diagnostic method that can timely detect and differentiate the condition and its causative agent.

All data in this paper are part of the results of master's thesis "Radiological approach to immunocompromised patient" written at the University Department of Health Studies, University of Split (24).

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Radiološka Obrada Infekcija kod Imunokompromitiranih Pacijenata

Sažetak

Imunokompromitiranost se definira kao stanje narušenog ili disfunkcionalnog imunološkog sustava, koji nije u stanju obraniti organizam od vanjskih patogena. Uzroci imunokompromitiranosti mogu biti prirođeni ili stečeni, a najogledniji primjer u svijetu jest virus humane imunodeficijencije. Imunokompromitirani bolesnik ima povećanu sklonost za razvoj infekcije, koja može biti uzrokovana patogenima poput gljivica, parazita, bakterija ili virusa.

Primjena odgovarajućih radioloških metoda u okviru dijagnostičke upotrebe ima važnu ulogu u ranom otkrivanju i liječenju različitih infektivnih i drugih bolesti koje su svojstvene imunokompromitiranim bolesnicima.

Imunokompromitirani pacijenti najčešće razvijaju oportunističke infekcije neurološkog sustava. S obzirom da neurološke promjene u početnom stadiju razvoja često ne budu uočene na CT pregledima, ponajviše se za pravovremenu detekciju bolesti koristi magnetska rezonancija, kao metoda najveće specifičnosti i osjetljivosti za navedena stanja. Prilikom snimanja MR-om bitno je koristiti više različitih predkontrastnih i dodatno postkontrastnih sekvenci, kako bi se sa sigurnošću mogle dokazati izrazito specifične neurološke infekcije, te njihova diferencijacija u odnosu na vrstu etiološkog čimbenika. Osim neuroloških komplikacija, imunokompromitirani pacijenti su vrlo skloni i razvoju respiratornih infekcija. Metoda izbora kod takvih komplikacija je svakako višeslojni CT, koji u ranoj fazi bolesti može detektirati i najmanje promjene unutar respiratornog sustava. Nakon inicijalne detekcije bolesti, za njeno daljnje praćenje, radiografska obrada torakalne regije predstavlja izuzetno snažan i pristupačan alat, koji sa svojom značajnom osjetljivošću može usmjeravati daljnji tijek liječenja.

Ključne riječi: HIV, imunodeficijencija, infekcija, radiologija