Neuroimaging of CNS infection in haematological malignancy: Important signs and common diagnostic pitfalls

Introduction

Haematological malignancies and precursor conditions affect a significant proportion of the UK population, with an estimated total prevalence rate of 548.8 per 100,000(1). Patients with haematological malignancy are at an increased risk of infection due to disease related disruption of immune function or treatment related immunosuppression, such as corticosteroids, chemotherapy, chimeric antigen receptor T cell (CAR T) therapy, or stem cell transplantation(2). The incidence of CNS infection following allogenic haematopoietic stem cell transplantation varies from 9-15% in the literature and is associated with reduced survival, necessitating early detection and accurate diagnosis(3-5).

Cerebrospinal fluid (CSF) analysis and biopsy remain the gold standard for the diagnosis of CNS infection(6, 7). However, neuroradiology has a vital role in patient management, especially in cases of diagnostic uncertainty or when definitive investigations are unremarkable; unobtainable or obtainable only after delay. Whilst computed tomography (CT) remains more accessible, magnetic resonance imaging (MRI) is superior for the direct evaluation of the brain parenchyma, meninges and the detection of complications of infection(8). MRI also has an established role as a non-invasive method of monitoring treatment response in these patients.

The detection and characterisation of infectious processes on MRI can prove challenging. In the context of immunosuppression, atypical and opportunistic pathogens are more prevalent than in the general population(3, 9). Whilst some pathogens are associated with more specific appearances, many share common imaging findings, and altered immune function can result in atypical or non-specific features(10). Furthermore, patients with haematological malignancies may develop other intracranial abnormalities during the course of their disease, such as treatment-related changes or thrombocytopaenia-related intracranial haemorrhage, which may confound both the clinical presentation and neuroimaging features(9).

This pictorial case series illustrates the MRI findings of a range of confirmed cases of typical and atypical CNS infections encountered over a 10-year period in adults with haematological malignancy at a large London tertiary haematology centre, of which the most commonly encountered pathogens were cytomegalovirus (CMV), toxoplasmosis, viral encephalitis, fungal infection, JC virus and pseudomonas. Here, we review common neuroimaging findings, identify features to help differentiate CNS infection from malignant CNS disease, and discuss frequently encountered diagnostic pitfalls.

Bacterial

Meningitis

The most common bacteria associated with pyogenic meningitis in the immunocompetent adult population are *Streptococcus pneumoniae* and *Neisseria*

meningitidis(11), however in the immunosuppressed host there is an increased incidence of pathogens such as tuberculosis (TB) and *Listeria monocytogenes*(12). The route of CNS infection is generally haematogenous, although may be secondary to geographic extension from the paranasal sinuses or orbits in some cases. MRI appearances can be normal, especially early in the disease course. The convexity or basal subarachnoid spaces may appear isointense on T1WI and hyperintense on FLAIR, with restricted diffusion of the exudative contents, and there can be associated leptomeningeal enhancement(8, 13). Whilst fine, linear enhancement is suggestive of a pyogenic bacterial aetiology, a nodular component is more indicative of tuberculous or fungal meningitis. Nodularity is also associated with malignant leptomeningeal disease, and often more focal in distribution than infective causes (Figure 1).

Complications, such as cerebral oedema and hydrocephalus, are relatively common(14). Choroid plexitis, ventriculitis, cerebritis, abscess and empyema formation can occur through direct extension, venous drainage or communication with perivascular spaces(13). Cerebrovascular complications include venous sinus thrombosis, venous infarction, vasculitis and arterial infarction (Figure 1). In the setting of meningitis, vasculitis is classically associated with tuberculous meningitis. Multifocal regions of vessel stenosis may be observed, particularly in the large intracranial arteries located within the basal cisterns and sylvian fissures, with or without evidence of perforator or large territorial infarction(15). Whilst MRI has an important role in the evaluation of the complications of meningitis, correlation with CSF is essential to ensure an accurate primary diagnosis(3). Neuroimaging has limited utility in this setting, and lymphoma, leukaemia and myeloma can manifest as leptomeningeal or pachymeningeal thickening and enhancement (Figure 1).

[Insert Figure 1]

Pyogenic abscess

Bacterial abscesses are relatively uncommon in the immunosuppressed patient. Cerebral pyogenic abscesses predominantly occur secondary to haematogenous spread, for example nocardiosis, or contiguous spread from a local source, but can also be secondary to head trauma or a neurosurgical procedure(16). When haematogenous in origin, the corticomedullary junction, particularly within the middle cerebral artery territory, is the most common location due to vascular flow dynamics and vessel calibre. The typical imaging features of a pyogenic abscess are that of a T1-hypointense, T2-hyperintense round or ovoid lesion within the brain parenchyma. The capsule is characteristically smooth and thin, T2-hypointense, and often relatively deficient in the segment adjacent to a ventricle (Figure 2)(8). Peripheral rim enhancement and homogeneous diffusion restriction within the abscess core is typical, and perilesional vasogenic oedema is variable but generally present(17). In this population, a lymphomatous deposit may also present as a discrete parenchymal mass with peripheral enhancement and diffusion restriction, but the region of diffusion restriction tends to be the enhancing component, rather than the necrotic core (Figure 2). A dual rim appearance of the capsule, with a low intensity peripheral and relatively hyperintense inner rim, on GRE T2* or SWI sequences, is a useful imaging feature that is relatively specific for a pyogenic aetiology(18) (Figure 3).

[Insert Figure 2]

[Insert New Figure 3]

Tuberculosis

There is an increased incidence of CNS TB in the context of malignancy and immunosuppressive medication. Symptoms may be subacute or non-specific, and a known history of TB is not always elicited(19). The intracranial manifestations of CNS TB include meningitis, with or without vasculopathy (discussed previously), tuberculoma and tuberculous abscess. The typical imaging findings of a tuberculoma are that of a solitary or multifocal parenchymal lesion, with intermediate to low signal intensity on T2WI, rim enhancement and variable perilesional vasogenic oedema(20). Lymphoma may demonstrate similar features, although tuberculomas are typically small in size. In contradistinction, the rarer tuberculous abscess demonstrates central T2WI/FLAIR hyperintensity, central diffusion restriction and is indistinguishable from a pyogenic abscess on standard imaging sequences(21). In the setting of suspected intracranial tuberculosis, imaging of the entire neuraxis should be considered to assess for evidence of spinal involvement.

Pseudomonas

Pseudomonas aeruginosa is an unusual cause of meningitis, is commonly hospital associated and typically related to neurosurgery(22, 23). It can also occur secondary to parameningeal extension from an adjacent structure, such as paranasal sinusitis (Figure 4)(24). In the context of sinus, orbital or skull base

disease, the cranial nerves, skull foramen and traversing structures should be interrogated for asymmetry, enlargement and pathological enhancement. Intracranial imaging appearances may reflect that of a meningitis, cerebral abscess or rarely, an extra-axial empyema depending on the route of infection. Associated cavernous sinus thrombophlebitis can present as enlarged, cavernous sinuses with internal filling defects on post-contrast imaging. In the presence of contiguous extension from paranasal sinus or orbital disease, other fungal pathogens such as mucormycosis should be also be considered in the differential diagnosis(25, 26).

[Insert Figure 4]

Parasitic

Cerebral toxoplasmosis

Cerebral toxoplasmosis is the most common parasitic CNS infection in allo-HSCT patients. Whilst generally occurring secondary to reactivation of latent *Toxoplasma gondii,* a ubiquitous intracellular parasite, primary infection following organ transplantation or ingestion of contaminated food may also occur(27). MRI commonly demonstrates multifocal T1-hypointense mass lesions, with a hyperintense or laminated appearance on T2WI/FLAIR and variable perilesional vasogenic oedema (Figure 5). There is a predilection for the basal ganglia and thalami, followed by the corticomedullary junction and posterior fossa. Rim enhancement, with an internal eccentric mural nodule -- the ‘eccentric target’ sign -- has been described(28, 29), although can be absent in the immunosuppressed state(30). Peripheral diffusion restriction may be observed, in contradistinction to

pyogenic abscesses, and evidence of peripheral haemorrhage is occasionally seen(31). In the immunocompromised, lymphoma can have similar imaging characteristics(32), although is more commonly subependymal in location, solitary and is not associated with haemorrhage prior to treatment (Figure 5). In cases of diagnostic uncertainty, MR perfusion, interval imaging following treatment or PET-CT can add value in the non-invasive setting.

[Insert Figure 5]

Viral

Viral encephalitis

The human herpes virus family includes herpes simplex virus 1 (HSV-1) and HSV-2, varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV) and human herpes virus (HHV-6, 7 and 8). These viruses are able to establish latency and reactivate periodically.

HSV-1 remains the most common cause of viral encephalitis in adults, although the incidence is relatively low in patients with haematological disorders(33). MRI features of HSV-1 encephalitis include bilateral, often asymmetric cortical and subcortical T2WI/FLAIR hyperintensities within the anterior and medial temporal lobes, inferior frontal lobes, insular cortex and cingulate gyri(13). In the immunocompromised state, the distribution can be more extensive, with widespread cortical involvement, brainstem or posterior fossa involvement(34). Patchy cortical/subcortical diffusion restriction may be seen early in the disease course(35),

and gyriform enhancement may occur in the subacute setting. Petechial haemorrhages are of variable appearance depending on the chronicity of the blood products, although commonly present as patchy regions of T1-hyperintensity and GRE T2*/SWI hypointensity with ‘blooming’(13). Curvilinear, gyriform haemorrhage can also be observed but is associated with the subacute and chronic phases, alongside local encephalomalacia(36).

HHV-6 is associated with post-transplant limbic encephalitis, with a median interval to presentation of 3 weeks(37). The imaging findings in HHV-6 are often limited to the mesial temporal lobes, with sparing of the parahippocampal gyri (Figure 6). Diffusion restriction is commonly observed, and enhancement(38) and haemorrhage are usually absent(39), in contradistinction to HSV encephalitis. EBV encephalitis is rarely encountered in the adult population, and is associated with non-specific findings, including mesial temporal lobe and subcortical white matter T2WI/FLAIR hyperintensities(40, 41). Mesial temporal lobe involvement is not typical for lymphoma(42) or leukaemia(43) and in this setting is suggestive of infection, although the various infective causes of encephalitis can be indistinguishable on MRI(44) (Figure 6). As the range of potential causative viruses is broad and the neuroimaging findings in encephalitis are often non-specific, correlation with CSF is required for confirmation of the causative organism.

[Insert Figure 6]

Cytomegalovirus (CMV) is generally seen in the immunosuppressed adult following reactivation of latent infection. The most common neurological

manifestations of CMV include retinitis, ependymitis and necrotising meningoencephalitis(45). Ependymitis is the most common intracranial presentation, and is associated with periventricular T1-hypointensity and T2-hyperintensity, with nodular thickening, enhancement and diffusion restriction of the affected ependyma (Figure 7)(46, 47). Hydrocephalus or a periventricular pattern of atrophy may be observed. Lymphoma is classically subependymal in distribution, and can have similar findings(48). Uncomplicated CMV retinitis is not resolvable on cross-sectional imaging and requires ophthalmic examination, although knowledge of its presence may raise clinical suspicion of associated CNS involvement in the context of subtle intracranial findings. Rarely, CMV can present as a diffuse encephalitis with widespread patchy hyperintense lesions on T2WI/FLAIR, or as a rim-enhancing, space occupying lesion with surrounding vasogenic oedema(49).

[Insert Figure 7]

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a form of subacute encephalitis caused by the John Cunningham (JC) polyomavirus, and is seen almost exclusively in the setting of severe immunocompromise. PML was first described in the context of chronic lymphocytic leukaemia, although is most widely associated with the HIV population(50). The presenting symptoms can be more indolent than other forms of acute encephalitis, including cognitive decline or altered mental state. The typical imaging appearances of PML are patchy regions of hyperintensity in the white matter of the parietal and occipital lobes, frontal subcortical white matter or

cerebellar peduncles on T2WI/FLAIR, with corresponding hypointensity on T1W images (Figure 8)(51). Involvement of the subcortical U-fibres creates a scalloped appearance. The distribution is typically bilateral and asymmetric, without significant cerebral atrophy. Contrast enhancement may be present in the context of immune reconstitution inflammatory syndrome, but is otherwise absent or faint. Diffusion restriction can be evident in the acute phase and is classically peripheral and with a leading edge(52), with a trend towards increased diffusivity in chronic lesions. Differentiation from treatment related changes is intimated by location, mass effect, diffusion restriction and the presence of enhancement. Whilst imaging plays a pivotal role in the diagnosis of PML, isolation of JC virus in the CSF is confirmatory. However, a negative PCR does not exclude the diagnosis.

[Insert Figure 8]

Fungal

Fungal infection of the CNS is rare and occurs more commonly in immunocompromised hosts. As a consequence of an altered immune response, the neuroimaging findings in fungal CNS infection are often non-specific and require interpretation in the context of clinical findings and known evidence of a causative fungus. The predominant invasive mould infection affecting the CNS in this patient cohort is *Aspergillus spp*,(53). Cerebral aspergillosis may occur due to direct intracranial extension from the paranasal sinuses, producing focal pachymeningeal thickening and parenchymal abnormalities in the adjacent frontal lobes. Alternatively, haematogenous spread from an extrinsic focus such the lungs may occur (Figure 9),

with a propensity for the corticomedullary junction and perforating arterial territories. CSF seeding is possible but less common. The imaging findings are diverse and include rim enhancing lesions, solid enhancing lesions (aspergilloma) or haemorrhagic foci(54). Although not always present, the characteristic appearance is a 'target' pattern of central hyperintensity and peripheral hypo/isointensity on T2WI, presumably secondary to blood breakdown products or iron products. In the context of a reduced immune response, there may be relatively little adjacent oedema and rim enhancement is typically weak or occasionally absent. Heterogenous, central diffusion restriction can be observed, in contrast to the intense, homogenous central diffusion restriction classically described in a pyogenic abscess. *Aspergillus* is angioinvasive and vascular complications such as stroke (both ischaemic and haemorrhagic) and focal microhaemorrhages may be present(55).

Other frequently encountered fungi include *Candida albicans* and *Cryptococcus neoformans*. *C. albicans* shares many similar imaging features with *Aspergillus spp,* including a propensity for perivascular dissemination which can mimic intravascular lymphoma. *C. neoformans* may present as a meningitis, parenchymal lesion (cryptococcoma), choroid plexitis or gelatinous pseudocysts in the distribution of the perivascular spaces, typically the basal ganglia(56, 57). When considering infection, T2-hyperintense pseudocysts are a feature unique to *C.neoformans*, and must be distinguished from incidental enlarged perivascular spaces.

[Insert Figure 9]

Pitfalls

Heterogenous appearances of CNS disease: The intracranial appearances of haematological malignancies, whether primary, metastatic or recurrent, are remarkably heterogeneous and may present with imaging findings similar to infectious processes. Correlation with advanced imaging techniques, FDG PET-CT, laboratory investigations and histological analysis are often required for definitive diagnosis(58, 59).

- *Parenchymal*: CNS lymphoma may appear as a rim enhancing mass lesion similar to pyogenic abscess or toxoplasmosis. Peripheral restricted diffusion can differentiate from pyogenic abscess and absence of haemorrhage in the wall can differentiate from toxoplasmosis.
- *Ependymal*: CNS lymphoma can also involve the ependyma, mimicking CMV ependymitis. Focal involvement, nodularity and the absence of intraventricular haemorrhage can aid distinction.
- *Leptomeningeal/pachymeningeal:* Bing-Neel syndrome, lymphoma, leukaemia and multiple myeloma can all involve the leptomeninges, but focal involvement with solid components and nodularity can aid distinction from bacterial meningitis.
    - *Dural:* Following intracranial biopsy, the development of an overlying extra-axial collection with pachymeningeal thickening and enhancement should raise concern for an empyema. However, pachymeningeal disease recurrence may have overlapping features and should remain in the differential.

Treatment-related effects: Treatment related neurotoxicity is common and includes chemotherapy related findings and the spectrum of radiation induced injuries(60).

- *Treatment-induced changes* manifest as bilateral T2WI/FLAIR white matter hyperintensities(61). Chemotherapy related posterior reversible encephalopathy syndrome (PRES) may exhibit cortical and subcortical white matter hyperintensities on T2WI/FLAIR, often with atypical features such as diffusion restriction and enhancement which can mimic infective processes such as PML(62). Recognition of involvement of the subcortical U-fibres is an important distinguishing feature.
- *Radiation-induced changes* can be broadly categorised into acute radiation injury, early delayed injury and long-term sequelae(63). Patients with delayed radiation injury may present with cognitive impairment and confluent, periventricular T2WI/FLAIR white matter hyperintensities. Late delayed radiation necrosis can appear expansile and mass like, with variable enhancement and central necrosis, mimicking recurrent disease. Consequently, correlation with the timing and type of treatment is important in ensuring accurate interpretation of neuroimaging findings.

Summary

Patients with haematological malignancy are a unique population who are at increased risk of CNS infection, including atypical infection. Clinical presentation is often vague and non-specific, and the underlying disease processes and treatment can confound image interpretation. Familiarity with the range and appearance of

CNS infections that may occur, alongside potential diagnostic pitfalls and relevant differential diagnoses in this cohort is vital and can have a profound impact on patient management and clinical outcome.

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