<table>
<thead>
<tr>
<th>Contents</th>
<th>Thrice Monthly Volume 9 Number 6 February 26, 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EDITORIAL</strong></td>
<td></td>
</tr>
<tr>
<td>1247 Interactive platform for peer review: A proposal to improve the current peer review system</td>
<td>Emile SH</td>
</tr>
<tr>
<td><strong>MINIREVIEWS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>ORIGINAL ARTICLE</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Case Control Study</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Retrospective Study</strong></td>
<td></td>
</tr>
<tr>
<td>1271 Analysis of hospitalization costs related to fall injuries in elderly patients</td>
<td>Su FY, Fu ML, Zhao QH, Huang HH, Luo D, Xiao MZ</td>
</tr>
<tr>
<td><strong>Clinical Trials Study</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Observational Study</strong></td>
<td></td>
</tr>
<tr>
<td>1304 Healthy individuals vs patients with bipolar or unipolar depression in gray matter volume</td>
<td>Zhang YN, Li H, Shen ZW, Xu C, Huang YJ, Wu RH</td>
</tr>
<tr>
<td>1318 Impact of metabolism-related mutations on the heart rate of gastric cancer patients after peritoneal lavage</td>
<td>Yuan Y, Yao S, Luo GH, Zhang XY</td>
</tr>
<tr>
<td><strong>CASE REPORT</strong></td>
<td></td>
</tr>
<tr>
<td>1329 Efficacy of afatinib in a patient with rare EGFR (G724S/R776H) mutations and amplification in lung adenocarcinoma: A case report</td>
<td>He SY, Lin QF, Chen J, Yu GP, Zhang JL, Shen D</td>
</tr>
</tbody>
</table>
Contents

1336  Esophageal superficial adenosquamous carcinoma resected by endoscopic submucosal dissection: A rare case report
   Liu GY, Zhang JX, Rong L, Nian WD, Nian BX, Tian Y

1343  Do medullary thyroid carcinoma patients with high calcitonin require bilateral neck lymph node clearance? A case report
   Gan FJ, Zhou T, Wu S, Xu MX, Sun SH

1353  Femoral epithelioid hemangioendothelioma detected with magnetic resonance imaging and positron emission tomography/computed tomography: A case report
   Zhao HG, Zhang KW, Hou S, Dai YY, Xu SB

1359  Noninvasive tools based on immune biomarkers for the diagnosis of central nervous system graft-vs-host disease: Two case reports and a review of the literature
   Lyu HR, He XY, Hao HJ, Lu WY, Jin X, Zhao YJ, Zhao MF

1367  Periodontally accelerated osteogenic orthodontics with platelet-rich fibrin in an adult patient with periodontal disease: A case report and review of literature
   Xu M, Sun XY, Xu JG

1379  Subtalar joint pigmented villonodular synovitis misdiagnosed at the first visit: A case report
   Zhao WQ, Zhao B, Li WS, Assan I

1386  Wilson disease — the impact of hyperimmunity on disease activity: A case report
   Stremmel W, Longerich T, Liere R, Vacata V, van Helden J, Weiskirchen R

1394  Unexplained elevation of erythrocyte sedimentation rate in a patient recovering from COVID-19: A case report
   Pu SL, Zhang XY, Liu DS, Ye BN, Li JQ

1402  Thoracic pyogenic infectious spondylitis presented as pneumothorax: A case report
   Cho MK, Lee BJ, Chang JH, Kim YM

1408  Unilateral pulmonary hemorrhage caused by negative pressure pulmonary edema: A case report
   Park HJ, Park SH, Woo UT, Cho SY, Jeon WJ, Shin WJ

1416  Osseous Rosai-Dorfman disease of tibia in children: A case report
   Vithran DTA, Wang JZ, Xiang F, Wen J, Xiao S, Tang WZ, Chen Q

1424  Abdominopelvic leiomyoma with large ascites: A case report and review of the literature
   Wang YW, Fan Q, Qian ZX, Wang JJ, Li YH, Wang YD

1433  Unusual presentation of granulomatosis with polyangiitis causing periaortitis and consequent subclavian steal syndrome: A case report
   Cho U, Kim SK, Ko JM, Yoo J

1439  Postoperative discal pseudocyst and its similarities to discal cyst: A case report
   Fu CF, Tian ZS, Yao LY, Yao JH, Jin YZ, Liu Y, Wang YY
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1446</td>
<td>Treatment of oral lichen planus by surgical excision and acellular</td>
<td>Fu ZZ, Chen LQ, Xu YX, Yue J, Ding Q, Xiao WL</td>
</tr>
<tr>
<td></td>
<td>dermal matrix grafting: Eleven case reports and review of literature</td>
<td></td>
</tr>
<tr>
<td>1455</td>
<td>Nonalcoholic fatty liver disease as a risk factor for cytomegalovirus</td>
<td>Khiatah B, Nasrollah L, Covington S, Carlson D</td>
</tr>
<tr>
<td></td>
<td>hepatitis in an immunocompetent patient: A case report</td>
<td></td>
</tr>
<tr>
<td></td>
<td>without fracture: A case report</td>
<td></td>
</tr>
<tr>
<td>1469</td>
<td>Intrahepatic cholangiocarcinoma is more complex than we thought: A</td>
<td>Zeng JT, Zhang JF, Wang Y, Qing Z, Luo ZH, Zhang YL, Zhang Y, Luo XZ</td>
</tr>
<tr>
<td></td>
<td>case report</td>
<td></td>
</tr>
<tr>
<td>1475</td>
<td>Congenital hepatic fibrosis in a young boy with congenital</td>
<td>Xiao FF, Wang YZ, Dong F, Li XL, Zhang T</td>
</tr>
<tr>
<td></td>
<td>hypothyroidism: A case report</td>
<td></td>
</tr>
<tr>
<td>1483</td>
<td>Polidocanol sclerotherapy for multiple gastrointestinal hemangiomas:</td>
<td>Yao H, Xie YX, Guo JY, Wu HC, Xie R, Shi GQ</td>
</tr>
<tr>
<td></td>
<td>A case report</td>
<td></td>
</tr>
<tr>
<td>1490</td>
<td>Gastrointestinal stromal tumor with multisegmental spinal metastases</td>
<td>Kong Y, Ma XW, Zhang QQ, Zhao Y, Feng HL</td>
</tr>
<tr>
<td></td>
<td>as first presentation: A case report and review of the literature</td>
<td></td>
</tr>
</tbody>
</table>
ABOUT COVER

Editorial Board Member of World Journal of Clinical Cases, Dr. Quach is an Associate Professor of Gastroenterology at the University of Medicine and Pharmacy at Hochiminh City, Viet Nam, where he received his MD in 1997 and his PhD in 2011. Dr. Quach has published more than 100 reviews and original papers in local and international journals. He has received several awards, including Outstanding Presentation at the Biannual Scientific Congress of Vietnamese Nationwide Medical Schools, Medal of Creativeness from the Vietnamese Central Youth League, etc. Currently, he serves as a Vice President of the Vietnam Association of Gastroenterology and Secretary General of the Vietnam Federation for Digestive Endoscopy. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of World Journal of Clinical Cases (WJCC, World J Clin Cases) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for WJCC as 1.013; IF without journal self cites: 0.991; Ranking: 120 among 165 journals in medicine, general and internal; and Quartile category: Q3. The WJCC’s CiteScore for 2019 is 0.3 and Scopus CiteScore rank 2019: General Medicine is 394/529.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Ji-Hong Liu; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lei Wang.
Noninvasive tools based on immune biomarkers for the diagnosis of central nervous system graft-vs-host disease: Two case reports and a review of the literature

Hai-Rong Lyu, Xiao-Yuan He, Hong-Jun Hao, Wen-Yi Lu, Xin Jin, Yu-Jiao Zhao, Ming-Feng Zhao

Abstract

BACKGROUND
Central nervous system graft-vs-host disease (CNS-GVHD) is a rare cause of CNS disorders after allogeneic hematopoietic stem cell transplantation. Currently, establishing a diagnosis of CNS-GVHD is challenging because the diagnostic criteria and diagnostic methods are not well defined and many confounding factors need to be ruled out.

CASE SUMMARY
Here, we present two patients with CNS-GVHD. Both patients with a history of acute GVHD or chronic GVHD developed neurological symptoms that could not be explained by other causes, and had abnormal cerebrospinal fluid (CSF) studies as determined by CSF and blood immune biomarker examinations, suggestive of suspected CNS-GVHD. Due to the lack of specific magnetic resonance imaging abnormalities and the rapid clinical deterioration of the patients, we did not attempt to perform a brain biopsy, but prompted the initiation of empirical immunosuppressive therapy. In view of the rapid and favorable response to local and systematic immunosuppressive treatment and the aforementioned neurologic manifestations together with CSF abnormalities and other negative findings, a final diagnosis of CNS-GVHD was made.
was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works upon this work non-commercially, and the use is non-commercial. See: http://creativecommons.org/License/ by-nc/4.0/

Manuscript source: Unsolicited manuscript

Specialty type: Medicine, research and experimental

Country/Territory of origin: China

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: September 12, 2020
Peer-review started: September 12, 2020
First decision: November 29, 2020
Revised: December 9, 2020
Accepted: December 16, 2020
Article in press: December 16, 2020
Published online: February 26, 2021

P-Reviewer: Jaing TH
S-Editor: Zhang L
L-Editor: Webster JR
P-Editor: Yuan YY

CONCLUSION
CSF and blood immune biomarker examinations facilitated the diagnosis of CNS-GVHD, which are particularly suitable for patients who are critically ill and require urgent treatment and for those who are unsuitable for invasive diagnostic procedures.

Key Words: Biomarkers; Immunology; Hematopoietic stem cell transplantation; Graft vs host disease; Central nervous system; Diagnosis; Case report

Core Tip: We systematically report the diagnostic methods used for central nervous system graft-vs-host disease and present our own diagnostic criteria. Furthermore, we propose that non-invasive tools, especially cerebrospinal fluid and blood immune biomarker examinations, facilitated the diagnosis of central nervous system graft-vs-host disease, which are particularly suitable for patients who are critically ill and require urgent treatment and for those who are unsuitable for invasive diagnostic procedures.

INTRODUCTION
Allogenic hematopoietic stem cell transplantation (allo-HSCT) is currently the only treatment strategy that has the potential to cure hematological malignancies. However, central nervous system (CNS) complications following transplantation pose a risk to patient survival[8-9]. Previous clinical studies reported that CNS complications occur in 11%-59% of patients after HSCT, including infections, drug-toxicity, disease relapse, secondary malignancies, vascular or metabolic abnormalities, as well as rare CNS graft-vs-host disease (CNS-GVHD)[10-11]. Two studies have reported that the incidence of immune-mediated neuropathy is 0.36% after stem cell transplantation and 1.04% after haploidentical HSCT, respectively[12-13]. Currently, establishing a diagnosis of CNS-GVHD is challenging because the diagnostic criteria and diagnostic methods are not well defined and many confounding factors need to be ruled out. Here, we report 2 cases of CNS-GVHD and review the literature on the currently available diagnostic methods for CNS-GVHD. We systematically report the diagnostic methods used for CNS-GVHD. It is suggested that the detection of immune biomarkers is necessary and has important clinical significance for the diagnosis of CNS-GVHD.

CASE PRESENTATION

Chief complaints
Case 1: A 15-year-old female complained of progressive vertigo, moderate headaches, nausea, vomiting, delusions, paroxysmal restlessness and insomnia. Simultaneously, she presented with a low fever.

Case 2: A 22-year-old male complained of vertigo, intermittent headache, impaired consciousness, confused speech, visual hallucinations, nausea, and vomiting.

History of present illness
Case 1: A 15-year-old female complained of progressive vertigo, moderate headaches, nausea, vomiting, delusions, paroxysmal restlessness and insomnia. Simultaneously, she presented with a low fever.
Case 2: A 22-year-old male complained of vertigo, intermittent headache, impaired consciousness, confused speech, visual hallucinations, nausea, and vomiting.

History of past illness

Case 1: The patient underwent a 5/10 human leukocyte antigen (HLA)-matched haploidentical donor peripheral blood stem cell transplant from her father in September 2018 for severe aplastic anemia with ASXL1 mutation. Approximately 4 mo after transplantation, the patient developed chronic GVHD (cGVHD) with lichen planus-like changes in the oral mucosa, which was treated with oral triamcinolone and topical dexamethasone mouthwashes.

Case 2: The patient underwent a 5/10 HLA-matched haploidentical peripheral blood stem cell transplant from his father in August 2018 for acute lymphoblastic leukemia with BCR/ABL P210 positive. The blood concentration of cyclosporine was maintained at a low level due to the presence of minimal residual disease. Approximately 2.5 mo after transplantation, he developed grade II acute GVHD (aGVHD) with rash and diarrhea based on the Glucksberg classification. He was treated with cyclosporine, sirolimus, and intravenous methylprednisolone (120 mg/d) for three days, and quickly achieved complete remission. The corticosteroid was then tapered and finally stopped.

Personal and family history

No relevant personal and family history.

Physical examination

Case 1: Physical examination revealed bradypsychia, posterior cord track syndrome and ataxia.

Case 2: Physical examination revealed impaired consciousness, confused speech and visual hallucinations.

Laboratory examinations

Case 1: CSF examination revealed no pleocytosis or abnormal glucose level, but showed elevated immunoglobulin G [IgG, 8.69 mg/dL (normal range 0.48-5.86 mg/dL)]. Then CSF and blood immune biomarker examinations were performed, including blood-brain barrier (BBB) permeability, IgG index, IgG synthesis rate (IgG-Syn), CSF and blood myelin basic protein (MBP), CSF and blood anti-myelin basic protein antibody (MBP.Ab), and CSF and blood anti-myelin oligodendrocyte glycoprotein antibody (MOG.Ab), which showed oligoclonal band type IV in blood and CSF (isoelectric focusing) and elevated IgG index (Figure 1). There was no evidence of hemolysis suggesting ongoing microangiopathy, and no serious kidney or liver dysfunction.

Case 2: CSF studies revealed pleocytosis [32 leucocytes/µL (normal range 0-5/µL)], lymphocytosis (89%), protein elevation [84.4 mg/dL (normal range 15-45 mg/dL)] and normal glucose level. There was no evidence of leukemia cells when the immunophenotype of CSF cells was detected. The CSF and blood immune biomarker examination showed positive oligoclonal band type IV in blood and CSF, elevated MBP and MBP.Ab in blood, and increased BBB permeability, IgG index and CSF IgG-Syn (Figure 1).

Imaging examinations

Case 1: A brain magnetic resonance imaging (MRI) ruled out the possibility of bleeding complications or post-transplantation lymphoproliferative disorders. A cervical MRI showed mild protrusion of C3-4, 4-5 and 5-6 intervertebral discs.

Case 2: A brain MRI did not reveal any abnormal lesions.

FINAL DIAGNOSIS

The final diagnosis of the presented two cases was CNS-GVHD.
Figure 1 Electrophoresis of oligoclonal band type IV in blood and cerebrospinal fluid. Immune biomarker examinations showed oligoclonal band type IV in the blood and cerebrospinal fluid (isoelectric focusing) in patient 1 and patient 2.

TREATMENT

Case 1
Tacrolimus was replaced by oral rapamycin and intravenous dexamethasone (15 mg/d) to control the neurological symptoms. The patient’s clinical symptoms quickly improved. The dose of dexamethasone was then tapered and decreased to an oral dose of 5.25 mg/d. After 20 d of treatment, her symptoms were relieved, and the patient was discharged. However, her neurological symptoms reappeared after 7 d, with progressive confusion, vertigo, delirium, visual hallucinations, suicidal tendency and temporarily impaired consciousness. Her performance status dropped to 4 points according to the Eastern Cooperative Oncology Group scoring criteria. All other findings were very similar to those at the time of initial diagnosis, including a repeat MRI. She was treated with 20 mg/d intravenous dexamethasone, 500 mg/d MMF and 20 g/d immunoglobulin for 5 d, and 10 mg/d oral ruxolitinib, in addition to anti-psychotic therapy with risperidone, and significant improvement was observed within 8 d. The dose of corticosteroid was then tapered. After 20 d of hospitalization, the patient was discharged and given oral triamcinolone (16 mg/d), MMF (500 mg/d) and ruxolitinib (10 mg/d). Unfortunately, she developed vertigo and diplopia again two months later. She received treatment with intravenous dexamethasone (20 mg/day for 5 d), CY (400 mg/m² every 2 wk) and rituximab (375 mg/m², once a week, 2 doses).

Case 2
He received empiric therapy with intrathecal dexamethasone (10 mg) once a week for 4 wk and achieved rapid improvement of neurological symptoms within 48 h.

OUTCOME AND FOLLOW-UP

Case 1
The patient has been followed up for three and a half months and her neurological symptoms have not reappeared. However, the CSF and blood immune biomarker examination still displayed an increase in the level of BBB permeability, neuron-specific enolase (NSE), S-100β, MBP and MBP.Ab. Therefore, she is currently receiving maintenance treatment with triamcinolone (24 mg/d), sirolimus, and ruxolitinib. In line with the clinical manifestations, laboratory findings, radiology, microbiology, and treatment response to immunosuppressive agents, the patient was diagnosed with CNS-GVHD.
Case 2

The patient has been followed up for three months and has been in good condition without recurrence of abnormal neurological symptoms.

DISCUSSION

GVHD is one of the most serious complications after allo-HSCT and occurs when donor T cells recognize and target alloantigens on healthy recipient tissues. aGVHD mainly targets the skin, gut, and liver, whereas cGVHD can affect most organs, including the CNS in rare cases. In the past, CNS involvement of GVHD was controversial, but more animal and human cases were histologically confirmed and revealed that there was frequent T cell infiltration, supporting the hypothesis of an immune-mediated CNS disease after allo-HSCT. However, CNS-GVHD remains very rare, and only a few cases have been reported. The clinical diagnosis of CNS-GVHD is extremely challenging for clinicians. In 2010, the neurological manifestations of cGVHD were described as a distinct entity in the Consensus Conference on Clinical Practice in cGVHD. The authors proposed the following mandatory criteria: the occurrence of neurological symptoms with cGVHD affecting other organs and CNS involvement without other explanations (i.e., without any infectious, vascular, drug toxicity, or metabolic etiologies). Other criteria were facultative: (1) Consistent brain MRI abnormalities; (2) CSF abnormalities (pleocytosis, elevated protein or IgG oligoclonal bands); (3) Pathological brain biopsy or postmortem examinations revealing GVHD lesions; and (4) A response to immunosuppressive therapy. The diagnosis of chronic CNS-GVHD can be made when both the mandatory and 2 facultative criteria are met. In the consensus conference, the occurrence of cGVHD affecting other organs is one of the mandatory criteria for diagnosing chronic CNS-GVHD. No diagnostic criteria for aGVHD have been defined in the literature. However, several case reports only had an aGVHD history without extra-CNS chronic GVHD during neurological symptoms, which was similar to our case 2. A study also demonstrated that CNS can be a direct target of alloreactive T cells following allo-HSCT in mice. These results suggest that early encephalitis after allo-HSCT may be a clinical presentation of CNS involvement of aGVHD. Thus, more clinical evidence and diagnostic methods are needed to further improve the diagnostic criteria for CNS-GVHD.

The Consensus Conference delineated 3 types of chronic CNS-GVHD, including cerebrovascular, CNS demyelinating, and immune-mediated encephalitis. Cerebrovascular disease can affect medium and large vessels, causing stroke-like episodes, or can involve CNS small vessels, inducing vasculitis. CNS demyelinating disease is described as having a relapsing-remitting course that resembles multiple sclerosis. Diagnosis is based on the white-matter lesions with gadolinium enhancement in MRI and CSF abnormalities. Immune-mediated encephalitis is the most difficult to diagnose due to negative imaging findings. The two cases reported here showed negative imaging, which made the diagnosis more difficult. The most common histological feature was the infiltration of CD3-positive T cell-dominant inflammatory cells in the perivascular space or within the vessel wall, whereas only scattered infiltrates were observed in the brain parenchyma. Most of these inflammatory cells were CD8-positive cytotoxic T cells. The infiltration of CD68-positive monocytes/microglia and HLA-DR-positive microglia has also been reported. However, brain biopsy is a painful and traumatic operation, and there may be no positive imaging results, making it impossible to determine the biopsy position, as in our cases. Therefore, we considered whether there are other valuable detection methods to assist the diagnosis of CNS-GVHD in the case of negative imaging and an inability to carry out brain biopsy.

Numerous studies have documented that the IgG index in the CSF is associated with many neurologic disorders. IgG-Syn is used to diagnose neurological diseases, such as multiple sclerosis. Bonnan et al. reported that IgG-Syn is a robust marker of persistent intrathecal inflammation, and its complete normalization should be one of the goals of future therapeutic strategies. Zhang et al. found that BBB permeability, CSF IgG-Syn and MOG.Ab were related to the occurrence of CNS demyelination. Another study described the presence of anti-neuronal antibodies directed against contactin-associated protein-like 2, a protein associated with voltage-gated potassium neurological channels, in patients with CNS-GVHD. Altogether, the CSF and blood immune biomarker examinations may act as another promising approach for diagnosing CNS-GVHD. CSF and blood immune biomarker examinations were...
performed in both our cases, including the oligoclonal band (isoelectric focusing), BBB permeability, IgG index, IgG synthesis rate (IgG-Syn), CSF and blood myelin basic protein (MBP), CSF and blood anti-myelin basic protein antibody (MBP.Ab), and CSF and blood anti-myelin oligodendrocyte glycopolypeptide antibody (MOG.Ab). In case 1, type IV oligoclonal band was positive and IgG index increased at the time of onset. After three and a half months, the immune markers were reexamined, the results showed that BBB permeability, NSE, S-100β, MBP and MBP.Ab increased, which did not appear at the time of onset. In case 2, the immune biomarker examination showed positive oligoclonal band type IV, elevated MBP and MBP.Ab in blood, and increased BBB permeability, IgG index and IgG-Syn. Therefore, it is necessary to detect immune biomarkers assessing neuronal, myelin and glial cell damage to diagnose CNS-GVHD, and multiple detection of immune biomarkers can improve the positive rate of the results and increase the accuracy of diagnosis.

Most CNS-GVHD cases had multiple hyperintense lesions in brain MRI, showing signs of healing, that were predominantly located in the white matter\(^1\). The MRI of leukoencephalopathy involves symmetric, high-intensity lesions in the white matter on T2-weighted imaging and fluid-attenuated inversion recovery. Punctate and curvilinear gadolinium enhancement can be seen along the path of the perforating medullary arteries\(^2\). We know that leukoencephalopathy can also result from many immunosuppressants, radiation therapy, and opportunistic infections after HSCT\(^3\). The MRI appearance of these forms of toxic leukoencephalopathy involves symmetric hyperintense lesions in the white matter on T2-weighted imaging and fluid-attenuated inversion recovery, but there is no punctate and curvilinear gadolinium enhancement\(^4\). It is worth noting that abnormal brain MRI findings do not appear in all CNS-GVHD cases. There are also several reports of patients with CNS-GVHD who presented only brain atrophy or who had no abnormalities in brain MRI\(^\text{5-10}^\text{1-22}\), similar to our cases. However, some reports without obvious lesions on MRI revealed diffuse alterations in brain activity on 18F-fluorodeoxyglucose (18F-FDG) PET-CT imaging in patients with CNS-GVHD. Brain 18F-FDG PET-CT demonstrated diffuse cortical and subcortical hypometabolism that completely normalized following immunosuppressive therapy\(^4\). Therefore, brain 18F-FDG PET-CT can provide supplemental information to facilitate the diagnosis of CNS-GVHD, especially in patients with normal MRI, and more research is warranted in the future. In addition, we believe that NGS is a time-saving and highly sensitive diagnostic method\(^23\). It can be used for the detection of pathogens and tumor cells, and plays an important role in the exclusion of CNS-GVHD.

In our cases, both patients with a history of aGVHD or cGVHD developed neurological symptoms that could not be explained by other causes, and had abnormal CSF studies as determined by CSF and blood immune biomarker examinations, suggestive of suspected CNS-GVHD. Due to the lack of specific MRI abnormalities and the rapid clinical deterioration of the patients, we did not attempt to perform a brain biopsy, but prompted the initiation of empirical immunosuppressive therapy. In view of the rapid and favorable response to local and systematic immunosuppressive treatment and the aforementioned neurologic manifestations together with CSF abnormalities and other negative findings, a final diagnosis of CNS-GVHD was made. Of note, all diagnostic methods related to CNS-GVHD used in this work are safe and fast.

Due to the rarity of CNS-GVHD after allo-HSCT, this complication has not been well recognized, leading to imperfect diagnostic criteria and diagnostic methods. Therefore, the diagnosis of CNS-GVHD by clinicians is challenging. Our research team proposed the following diagnostic criteria for CNS-GVHD: Prerequisites are the occurrence of cGVHD or a history of aGVHD leading to central nervous system involvement as the main manifestation, with no other explanation of CNS abnormalities (no infectious, vascular, drug toxicity or metabolic etiology, etc.). Required conditions include: (1) Brain MRI suggests white matter demyelinating lesions; (2) CSF abnormalities, including pleocytosis, elevated protein or abnormalities in CSF biomarkers (positive IgG oligoclonal bands type IV or V, increased IgG index, IgG-Syn, MBP, MBP.Ab, S100β, NSE, etc.); (3) Pathological brain biopsy or postmortem examinations revealing GVHD lesions; and (4) Immunosuppressive therapy is effective. A definite diagnosis of CNS-GVHD can be made by satisfying these prerequisites and three of the required conditions, and possible diagnosis by satisfying the prerequisites and two of the required conditions.
CONCLUSION

This report systematically describes the diagnostic methods for CNS-GVHD and presents our own diagnostic criteria. Furthermore, non-invasive tools, especially CSF and blood immune biomarker examinations, are proposed to facilitate the diagnosis of CNS-GVHD, which is particularly suitable for patients who are critically ill and require urgent treatment and for those who are unsuitable for invasive diagnostic procedures. All clinical cases should be documented to better define this entity and improve the diagnostic criteria and diagnostic methods.

ACKNOWLEDGEMENTS

We thank our patients for participating in this study.

REFERENCES


