An underrated complication of the organs' transplantations

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Sabino Luzzi[1,2], Marco Demasi[1], Alice Giotta Lucifero[1], Anna Simoncelli[4], Sergio Carnevale[5], Patrizia Morbini[6], Alberto Maria Crovace[7,8], Nicola Tartaglia[9], Antonio Ambrosi[9]

[1] *Neurosurgery Unit, Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy*
[2] *Neurosurgery Unit, Department of Surgical Sciences, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[3] *School in Experimental Medicine, Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy*
[4] *Diagnostic Radiology, Interventional Radiology and Neuroradiology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[5] *Anatomic Pathology Section, Cerba Health Care Italia, Milano (MI)*
[6] *Unit of Pathology, Department of Molecular Medicine, University of Pavia, IRCCS Policlinico San Matteo Foundation, Pavia, Italy*
[7] *Department of Emergency and Organ Transplantation, University of Bari "Aldo Moro", Bari, Italy*
[8] *Department of Veterinary Medicine, University of Perugia, Perugia, Italy*
[9] *Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy*

An underrated complication of the organs' transplantations

INTRODUCTION: *Tacrolimus is routinely used to prevent rejection after organs' transplantation. Neurotoxicity is underrated side effect, where no typical clinical, radiological, or histopathological patterns have yet been found. The present study is targeted to a review of the literature on tacrolimus-induced neurotoxicity secondary to organs' transplantation, aimed to its prompt diagnosis.*
MATERIALS AND METHODS: *Multiple PubMed searches were performed to review relevant articles regarding tacrolimus-induced neurotoxicity. An illustrative case is also presented.*
RESULTS: *Twenty articles published between 1997 and 2019 were identified and reviewed. Clinical manifestations of tacrolimus-induced neurotoxicity varied. MRI showed subcortical white matter involvement in most cases. Symptoms and radiological signs occurred at various drug dosages and blood tacrolimus levels. Tacrolimus discontinuation resulted in disappearance or marked reduction of neurological symptoms and imaging lesions in every case.*
CONCLUSION: *Neurotoxicity is an underrated reversible side effect of chronic tacrolimus administration after organs' transplantation. Its prompt diagnosis, based on T2 and FLAIR MRI sequences neuroimaging combined with stereotactic biopsy, allows the discontinuation of the drug and a recovery of the patient in most of the cases.*

KEY WORDS: Stereotactic Biopsy, Neurotoxicity, Tacrolimus, Transplant Complications, Transplantation, Tumor-like Lesion

Introduction

Tacrolimus, also known as FK-506, is an immunosuppressant macrolide derived from *Streptomyces tsukubaensis* commonly used to prevent rejection after solid organs and hematopoietic stem cell transplantation [1,2]. Various neurological and renal side effects of tacrolimus are well-known. Neurotoxicity was first reported in 1996 by Hinchey et al. [3] as posterior reversible encephalopathy syndrome (PRES); other tacrolimus-related neurological side effects include sensory and motor dysfunction, tremor, neuralgia, peripheral neuropathy, seizure, cortical blindness, cerebellar ataxia, vasculopathy and psychiatric disorders [4,5]. The symptoms of tacrolimus-induced neurotoxicity are non-specific and similar to the onset of other tumoral or vascular neurosurgical pathologies [6-13]; therefore, imaging studies are fundamental in making the diagnosis. Magnetic resonance imaging (MRI) of the brain is the most sensitive modality to detect and descri-

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Correspondence to: Alice Giotta Lucifero M.D., Neurosurgery Unit, Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Polo Didattico "Cesare Brusotti", Viale Brambilla, 74 - 27100, Pavia, Italy (e-mail: alicelucifero@mail.com)

ABBREVIATIONS

ACA: Anterior Cerebral Artery
CMV: Cytomegalovirus
CNS: Central Nervous System
CSF: Cerebrospinal Fluid
CT: Computed Tomography
FLAIR: Fluid-Attenuated Inversion Recovery
MCA: Middle Cerebral Artery
MRA: Magnetic Resonance Angiography
MRI: Magnetic Resonance Imaging
MRS: Magnetic Resonance Spectroscopy
PRES: Posterior Reversible Encephalopathy Syndrome

be tacrolimus-induced neurotoxicity, which typically appears as white matter lesions predominantly in the posterior cerebral region; however, exceptions may be found [14,15]. Rarely, tacrolimus-induced encephalopathy can resemble a tumor-like lesion [16]. The prompt recognition of neurotoxicity due to tacrolimus is vital, because discontinuing the drug is the appropriate treatment. Therefore, we conducted a review of the literature on tacrolimus-induced neurotoxicity after the organs' transplantation in order to improve the prompt diagnosis of this underrated complication.

Materials and Methods

A comprehensive literature review of articles regarding tacrolimus-induced neurotoxicity published since 1997 was performed via multiple PubMed database searches using the following keywords: "Neurotoxicity", "Stereotactic Biopsy", "Tacrolimus", "Transplant Complications", "Transplantation", and "Tumor-like Lesion". Only papers published in English were considered, and we focused in particular on central nervous system (CNS) lesions. Results were further filtered according to titles and abstracts to select the most relevant articles. In addition, we also present a case from the personal experience.

Results

Literature Search

Twenty articles were selected as result of the literature search (Table I). They all dealt with the role of tacrolimus in triggering neurological symptoms in patients who underwent various types of transplant (heart, kidney, liver, bone marrow, pancreatic islet, and lung). In 17 articles, a radiological correlate is described; histopathological study was performed in 2 articles.

Clinical Findings

Regarding clinical findings of tacrolimus-induced neurotoxicity, it was not possible to find a common denominator. Patients presented with a wide range of symptoms according to the involved anatomical site, which was most commonly the subcortical white matter. Fifty-five percent of patients complained of non-specific disturbances such as headache, confusion, agitation and altered mental status. Motor dysfunction was present in 25%; visual impairment and seizures occurred in 20%. Cerebellar ataxia and related deficits such as dysmetria, dysdiadochokinesis, and unsteady gait were present in 15%. Language deficits occurred in 10%.
In all articles, patients experienced rapid improvement or even disappearance of the neurologic symptomatology after tacrolimus discontinuation.

Radiological Findings

MRI was the radiological exam of choice, although with several limits. In almost all cases, T1- and T2-weighted magnetic resonance imaging was obtained and completed with fluid attenuated inversion recovery (FLAIR) sequences. Most commonly, non-specific anomalies were observed in the subcortical white matter, but isolated lesions involving the brain stem or cerebellum were also found. These anomalies were clearly and widely identified as hyperintense signal abnormalities on T2-weighted and FLAIR sequences.
In a case of tacrolimus-related polyneuropathy, no evidence of spinal cord or cauda equina pathology was detected on thoracic and lumbosacral MRI [15]. In another case, MRI and magnetic resonance angiography (MRA) showed an acute right hemispheric cerebral infarction and multiple stenoses of the anterior cerebral artery (ACA) and middle cerebral artery (MCA), suggesting that tacrolimus may cause vascular pathology [4]. Computed tomography (CT) was used in two cases and no lesion was described. Further radiological investigation was not specified.

Tacrolimus dosage and blood level

Tacrolimus dosage was not reported in 9 cases; in the remaining ones, different doses were reported. In 6 cases, tacrolimus blood level was not reported. The literature demonstrated that neurotoxicity may occur regardless of tacrolimus blood level, since neurotoxicity occurred in patients with tacrolimus level above and below the normal range (5-20 ng/mL), as well as in 15 patients with a normal tacrolimus level.

Table I - *Literature Review of Tacrolimus-Induced Neurotoxicity*

Author	Patients #	Age (years)/ Gender	Transplanted organ	Tacrolimus dosage	Blood level of tacrolimus after onset of neurological symptoms (ng/mL)*	Clinical findings	Radiological findings	Histopathology	Radiological evolution after discontinuation of tacrolimus
Ganeshakrishnan K. Thyagarajan et al. (1997)[7]	1	59/F	Lung	Not reported	13	Confusion, expressive aphasia, memory loss, headache	MRI study with diffuse changes in the subcortical white matter and grey matter bilaterally on T2 sequences, with meningeal enhancement	Results consistent with leukoencephalopathy	No more sign on MRI after 2 weeks
R. E. Steg et al. (1999)[9]	1	54/F	Bone marrow	Not reported	20	Confusion, spatial disorientation, cortical blindness with visual defects and a visual acuity of light perception	MRI study with abnormal signals in the posterior parietal and temporal areas bilaterally	No biopsy has been performed	MRI was not repeated
Patrick J. Oliverio et al. (2000)[10]	1	30/F	Bone marrow	0.02 mg/kg/ day	Within the therapeutic range (value not reported)	Diplopia, nystagmus, visual hallucinations and internuclear ophthalmoplegia	MRI study with bilaterally symmetric areas of increased signal on T2-weighted and FLAIR sequences within midbrain, pons and medulla oblongata	No biopsy has been performed	No more sign on RMI after 10 days
A. K. Scheel et al. (2001)[11]	2	59/M; 23/F	Kidney	Not reported	Not reported	Multiple complex partial seizures; Tremor of both hands, paranoid psychosis	No sign on CT, diagnostic assessment not specified	No biopsy has been performed	Not specified
Pierfrancesco Veroux et al. (2003)[12]	2	34/F; 24/M	Kidney	Starting with 0.1 mg/kg/ day, then various adjustments	12–14 in the first month post-transplant, then 8-10	Tonic-clonic seizures	No sign on CT, diagnostic assessment not specified	No biopsy has been performed	Not specified
Joseph Kaleyias et al. (2006)[5]	1	20/F	Kidney	7 mg twice a day	Not more than 35	Subacute cerebellar ataxia, dysarthria and tremulousness	MRI study with hyperintensity in the cerebellum, predominantly in the vermis, on T2 weighted and FLAIR sequences	No biopsy has been performed	Marked improvement in cerebellar hyperintensities on MRI after 3 months
Tatiana Froud et al. (2006)[13]	1	32/F	Pancreatic islet	Not reported	3-5	Insomnia, headache, confusion, episode of memory lapses	MRI study with multiple nonspecific punctuate foci in the periatrial white matter of both parieto-occipital hemispheres, more evident on T2 and FLAIR sequences	No biopsy has been performed	Minimally improved frame on MRI after 4 and 11 months

(segue)

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Author	Patients #	Age (years)/ Gender	Transplanted organ	Tacrolimus dosage	Blood level of tacrolimus after onset of neurological symptoms (ng/mL)*	Clinical findings	Radiological findings	Histopathology	Radiological evolution after discontinuation of tacrolimus
Kacznarek et al. (2007)[14]	1	31/M	Heart	3 mg twice daily in the first year after transplant, then 1 mg twice a day during the 9-year follow up	15	Cerebellar ataxia, with unsteady gait and dysdiadochokinesis	MRI study with symmetric hyperintense signals at the level of an atrophic cerebellum on T2 sequences	No biopsy has been performed	Not specified
Seung-Han Lee et al. (2008)[15]	2	19/F; 40/F	Bone marrow	Not reported	16.5; 265.9	Anxiety, agitation, insomnia, short-term memory loss, disorientation	MRI study with abnormal signal intensity in bilateral hippocampal areas on T2 and FLAIR sequences	No biopsy has been performed	Decreased abnormalities on MRI after 3 weeks
Annick De Weerdt et al. (2008)[6]	1	44/F	Liver and pancreas	0.04-0.08 mg/kg/day	12	Progressive paraparesis in both proximal and distal muscles, areflexia in the lower limbs	No sign of myelopathy or disturbance of the cauda equina on MRI of the thoraco-lumbo-sacral spine	No biopsy has been performed	Not specified
P. Hodnett et al. (2008)[2]	1	18/F	Bone marrow	Not reported	Not reported	Seizures, altered mental status and headache	MRI study with bilateral symmetrical areas of high signals intensities in the subcortical white matter and cerebellar high signal intensities involving the white matter and foliae on T2-weighted and FLAIR sequences	No biopsy has been performed	Minor residual areas of increased white matter signal intensity in the right frontal lobe but complete resolution of all cerebellar and parieto-occipital subcortical white matter hyperintensities on MRI after 4 weeks
Paolo Aridon et al. (2009)[8]	1	57/M	Liver	3 mg/day	Not reported	Severe pyramidal paresis involving the face and the left limbs together with moderate hypaesthesia in the left side of the body	MRI study with a large hyperintense lesion in the white matter of the right hemisphere on T2 and FLAIR sequences	Widespread sub-acute necrotising process without lympho-monocytic infiltrate	No more sign on MRI after 6 months
Woo-Hyung Kwun et al. (2011)[4]	1	11/F	Kidney	0.2 mg/kg/day	19.7	Headache, left motor weakness	MRI and MRA study with acute cerebral infarction of subcortical white matter of the right hemisphere and multiple stenosis of both ACA and MCA	No biopsy has been performed	Improvement of multifocal acute infarction and no stenosis of either ACA or MCA (time not specified)

(segue)

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Author	Patients #	Age (years)/ Gender	Transplanted organ	Tacrolimus dosage	Blood level of tacrolimus after onset of neurological symptoms (ng/mL)*	Clinical findings	Radiological findings	Histopathology	Radiological evolution after discontinuation of tacrolimus
Kyota Fukazawa et al. (2011)[16]	1	62/F	Liver	Not reported	7-8	Aphasia, apraxia, anarthria, paraplegia	MRI study with a 1 cm hyperintense lesion in the center of the pons (central pontine myelinolysis) on T2 sequence	No biopsy has been performed	No more sign on MRI after 5 months
Geru Wu et al. (2013)[17]	1	69/M	Kidney	5 mg twice a day	48.1	Weakness in distal portion of both legs with bilateral foot drop, unsteady gait, disoriented to time	Chronic microvascular ischemic changes not imputable to tacrolimus	No biopsy has been performed	Not specified
Walid El Moghazy et al. (2013)[18]	1	54/M	Liver	Not reported	Not reported	Encephalopathy, deterioration of mental status, locked-in-syndrome	RMI study with central pontine myelinolysis	No biopsy has been performed	Not specified
Altaf Saadi et al. (2016)[19]	1	52/M	Liver	Not reported	6.3 – 9.0	Headache, diplopia, gait unsteadiness, nystagmus, dysmetria, gait ataxia	MRI study with extensive FLAIR and T2 hyperintensity signal affecting pons and middle cerebellar peduncles bilaterally	No biopsy has been performed	No more sign on MRI after 6 months
Aniruddh Kapoor et al. (2017)[20]	1	37/F	Heart	6 mg twice a day	8.4	Generalized tonic-clonic seizures, headache	MRI study with T2 high signal intensity within the cortex of bilateral frontal and parietal lobes and subtle signs of abnormality in the temporal and occipital cortices	No biopsy has been performed	No more sign on MRI (time not specified)
Barbaros S. Karagun et al. (2018)[21]	1	13/M	Bone marrow	0.01 mg/kg/ day	Within the therapeutic range (value not reported)	Diplopia, ptosis, weakness of eye adduction unilaterally	MRI study with bright signals in the occipital and parietal subcortical white matter and in the cerebellum on T2-weighted and FLAIR images	No biopsy has been performed	Not specified
Carmelo Luca Smeralda et al. (2019)[22]	1	60/F	Kidney	3.5 mg/day	7.7	Headache	MRI study with diffuse and symmetric hyperintensity widely involving supratentorial and infratentorial white matter on T2 and FLAIR sequences	No biopsy has been performed	Neuroradiological improvements after 5 months

*Normal tacrolimus blood level: 5-20 ng/mL. ACA: Anterior Cerebral Artery; CT: Computed Tomography; F: Female; FLAIR: Fluid-Attenuated Inversion Recovery; M: Male; MCA: Middle Cerebral Artery; MRA: Magnetic Resonance Angiography; MRI: Magnetic Resonance Imaging.

Pathology

Biopsy was performed in only 2 reported cases. In the first case, the tissue was consistent with leukoencephalopathy; immunohistochemical staining for CD68 and glial fibrillary acid protein (GFAP) showed profound microglial activation and hypertrophy and a marked increase in the number of activated astrocytes within the white matter [17]. Pathological examination in the second case showed a widespread subacute necrotizing process without lymphomonocytic infiltrate [18].

Diagnostic Criteria

Among the articles reviewed, there were no standard or shared diagnostic criteria; tacrolimus-induced neurotoxicity appears to be a diagnosis of exclusion. Routine laboratory testing was commonly performed, including blood tests, cerebrospinal fluid (CSF) analyses, renal and hepatic function testing, and others based on individual patient symptoms. MRI was the primary radiologic diagnostic modality utilized except for 2 cases which underwent CT as noted above. Tacrolimus discontinuation proved to be both treatment and the definitive diagnostic test.

Illustrative Case

A 68-year-old man underwent heart transplantation due to post-ischemic dilated cardiomyopathy. His past medical history was significant for benign prostatic hypertrophy, osteoporosis, rheumatoid arthritis, obstructive sleep apnea syndrome, intention tremor affecting both upper limbs, two acute myocardial infarctions, solitary pulmonary nodule, and infectious cytomegalovirus (CMV) reactivation treated with ganciclovir. Post-operative immunosuppressive therapy consisted of tacrolimus and mycophenolate (daily dose, 7 mg and 1080 mg, respectively). Two months after transplantation, he presented with aphasia and left hemiplegia followed by generalized tonic-clonic seizures. The non-contrast enhanced CT brain was performed, showing a right frontal-insular subcortical hypodensity (Fig. 1). Subsequently, Gadolinium contrast-enhanced MRI showed an intra-axial frontal-insular lesion and involvement of the surrounding white matter (Fig. 2).

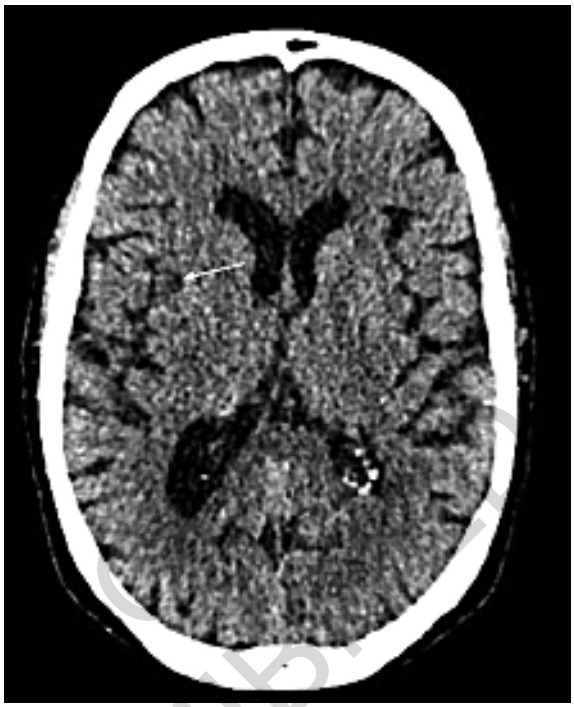

Fig. 1: Non-contrast brain CT: the arrow indicates a right focal cortical-insular hypodensity.

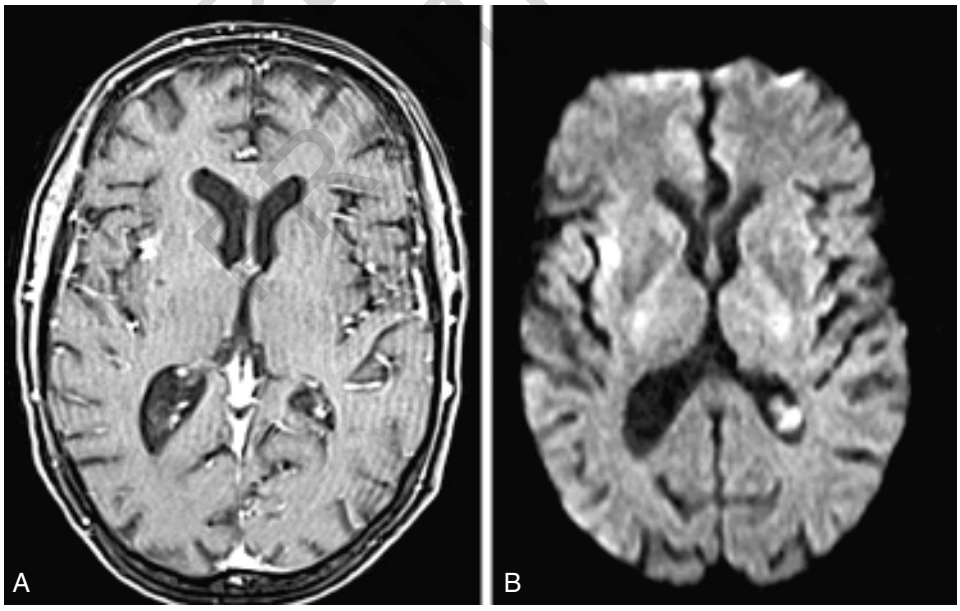

Fig. 2: Right focal cortical-insular enhancement. (A) T1-weighted magnetic resonance imaging corresponds to restricted diffusion on diffusion-weighted sequences (B) in the region of CT hypodensity.

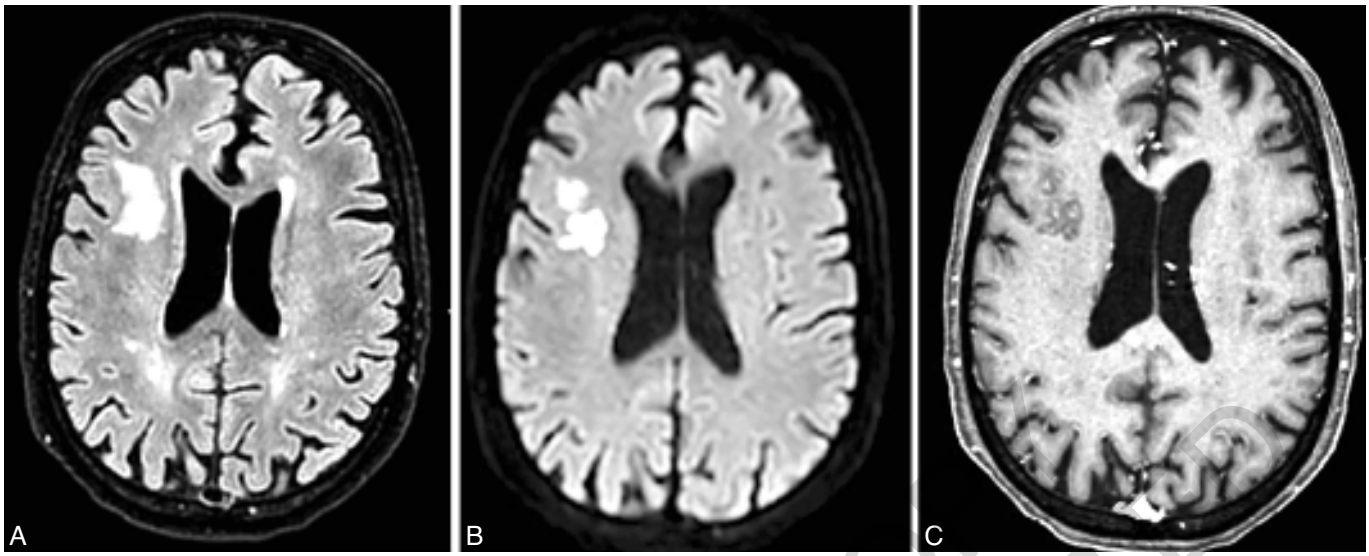

Fig. 3: (A) FLAIR imaging showed a multifocal confluent hyperintensity in the right frontal subcortical white matter, which corresponds to restricted diffusion on diffusion-weighted sequences (B), and patchy enhancement on contrasted T1-weighted imaging (C).

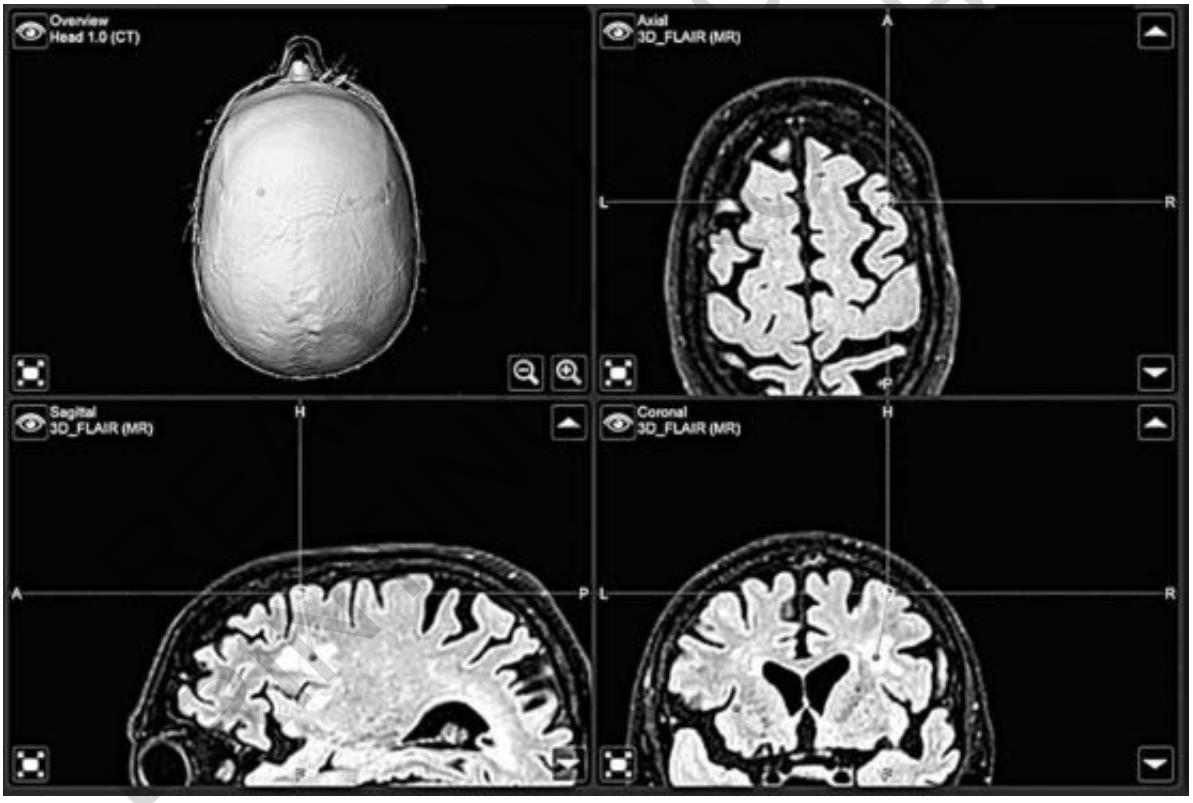

Fig. 4: Intra-operative trajectory for frameless stereotactic biopsy in axial, sagittal and coronal plane.

A transthoracic echocardiogram was performed, but no cardiac vegetations were found. During his clinical course, the patient appeared feverish and minimally responsive; clonus was present in the upper and lower limbs. At this time, the tacrolimus level was 19.7 ng/mL (therapeutic range, 15-20 ng/mL). Blood cultures pointed out first the presence of *Pseudomonas aeruginosa*, then *Klebsiella pneumoniae*; both were treated with appropriate antibiotic therapy. Renal and hepatic function tests were normal. CSF analyses were also normal; JC virus testing was negative.

The patient underwent to a radiological follow-up based on a wait-and-see approach. After two weeks a new contrast-enhanced MRI was performend, showing an increase of the volume of the lesion (Fig. 3).

As tacrolimus-induced neurotoxicity was suspected, tacro-

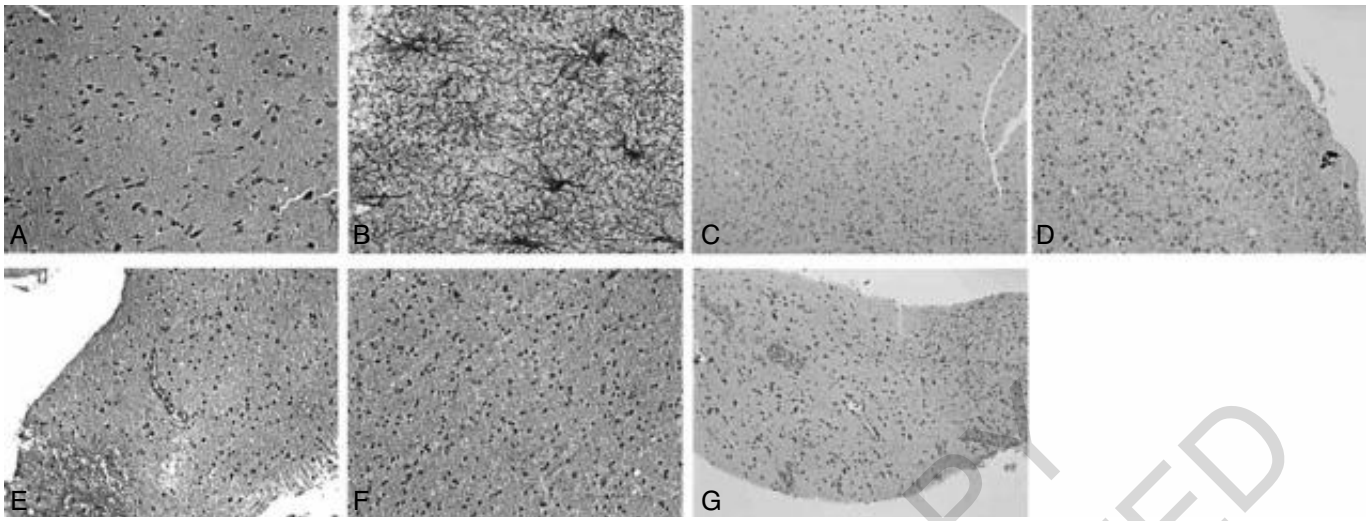

Fig. 5: Histologic findings of illustrative case. (A) W2-20X: HE, 200x. Only minimal changes are present in these lesions. (B) GFAP-40X: GFAP IHC, 400x. No activation or proliferation of glial cells is visible. (C) KI67-10X: Mib1/Ki-67 IHC, 100x. No evidence of actively cycling cells. (D) LCA20X: LCA/CD45 IHC, 200x. No lymphocyte infiltration of the parenchyma (control cells in a capillary). (E) W5-20X: HE, 200x. Capillaries are visible and intact with no evidence of vasculitis. (F) W1-20X: HE, 200x. No neuronal cell modifications are present. (G) CMV-10X: CMV IHC, 100x. No evidence of CMV infection.

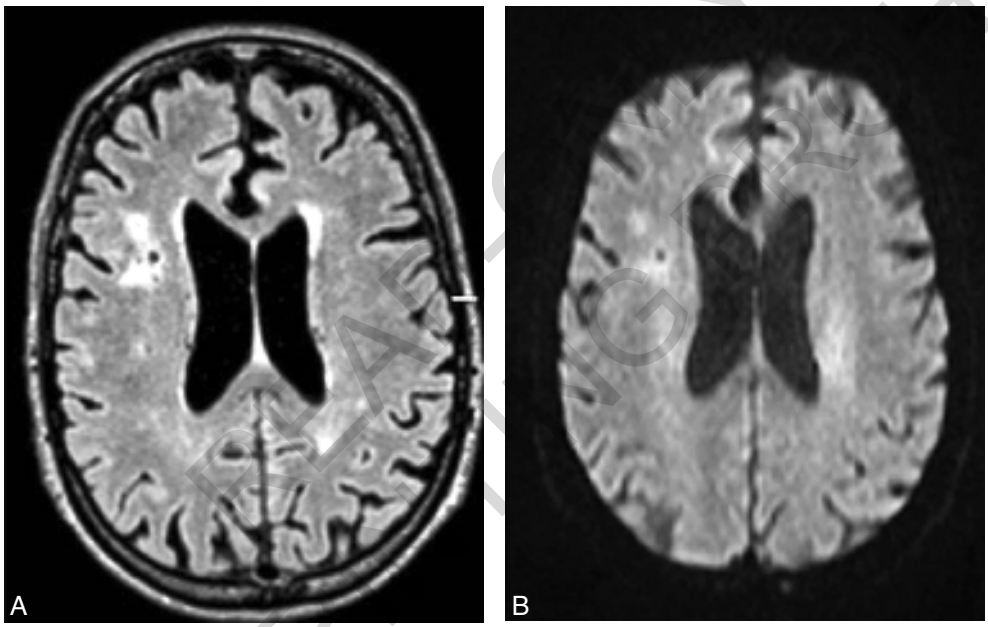

Fig. 6: (A) FLAIR imaging showed volume reduction of the frontal lobe white matter alteration with disappearance of restricted diffusion and enhancement on diffusion-weighted sequences (B).

limus was discontinued and replaced with everolimus.

In the meantime, a stereotactic brain biopsy (Fig. 4) was performed to obtain cortical and subcortical brain tissue samples. Pathologic examination showed no evidence of infectious process, lymphocyte infiltration, gliosis, or neoplastic proliferation; immunohistochemical stains for CD45, p53, mutant IDH-1 protein, and Ki-67 were negative.

Although other reported biopsied cases showed important histopathological changes in brain parenchyma, these were minimal in our case (Fig. 5A). GFAP immunochemistry (Fig. 5B) highlighted a lack of activation of neuroglial cells, which was confirmed by a Ki-67 proliferation index near zero (Fig. 5C). LCA/CD45 was useful to rule out lymphocyte infiltration of the parenchyma (Fig. 5D), and no vasculitis was found (Fig. 5E). No dysplastic or hypotrophic modification of neurons was visualized (Fig. 5F). Immunochemistry with anti-CMV antibodies (Fig. 5G) was performed to rule out viral reactivation. These findings suggest that only minimal changes may be found in a biopsy specimen from a discrete cerebral lesion in a patient receiving active treatment with tacrolimus.

Post-operative MRI showed a volume reduction of the

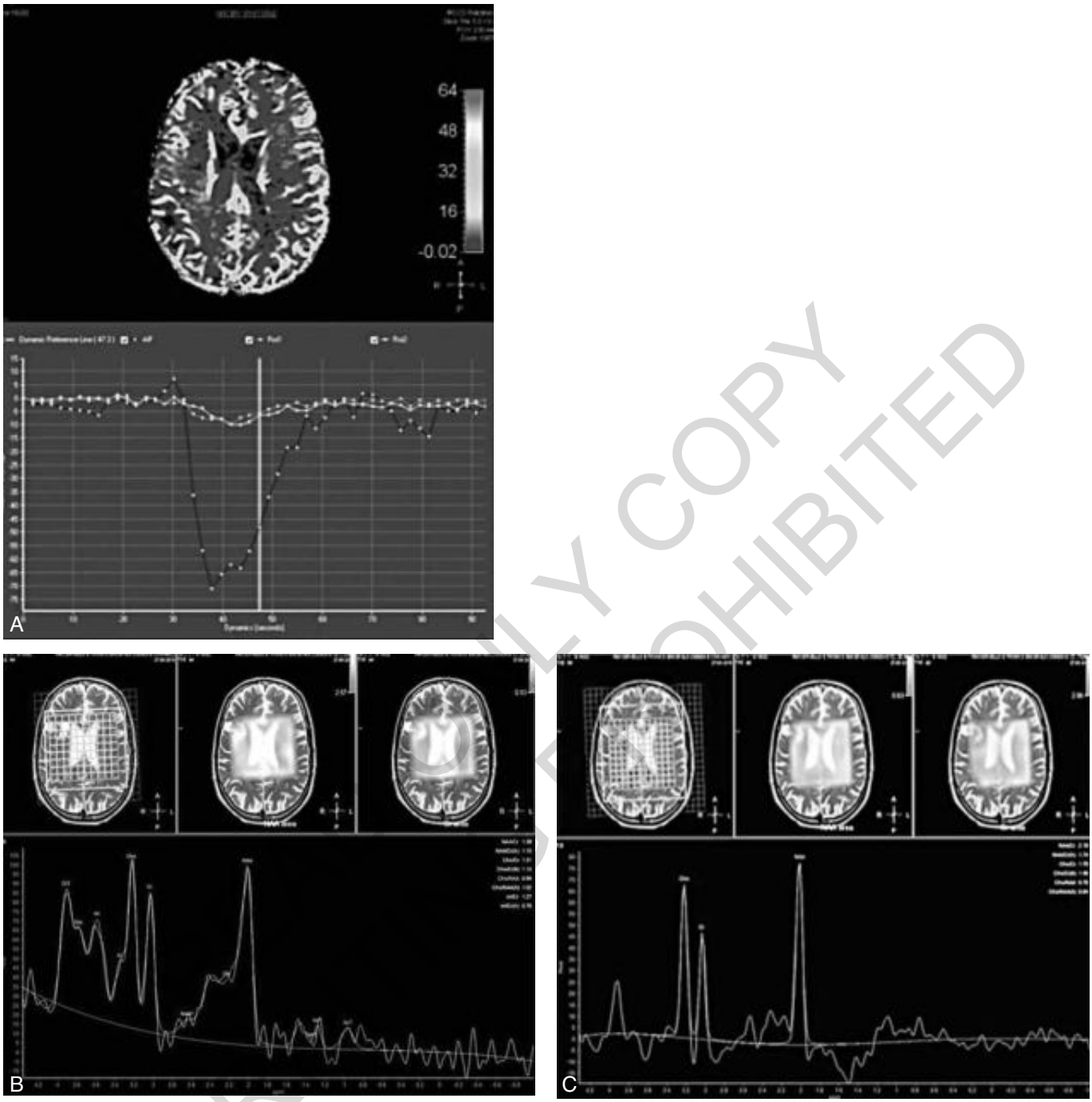

Fig. 7: Advanced brain MRI techniques. (A) Perfusion T2 MRI showed no significant difference in cerebral blood volume between the lesion and normal cerebral parenchyma. Magnetic resonance spectroscopy showed moderate elevation of the Cho/Cr ratio without inversion of the Cho/Naa ratio at short (B) and intermediate (C) echo times.

frontal lobe white matter alteration on FLAIR sequences. Diffusion-weighted and post-contrast T1-weighted sequences showed disappearance of restricted diffusion and enhancement, respectively (Fig. 6). Perfusion T2 MRI showed that regional cerebral blood volume (CBV) within the lesion was comparable to normal (Fig. 7A). Magnetic resonance spectroscopy (MRS) showed moderate elevation of the Cho/Cr ratio without inversion of the Cho/Naa ratio at short and intermediate echo times (Figs. 7B, C).

After tacrolimus discontinuation, the patient clinically improved and became symptom-free. MRI two months later showed absence of the cortical lesion and a marked volume reduction of the white matter alteration (Fig. 8). Currently he is undergoing regular follow up.

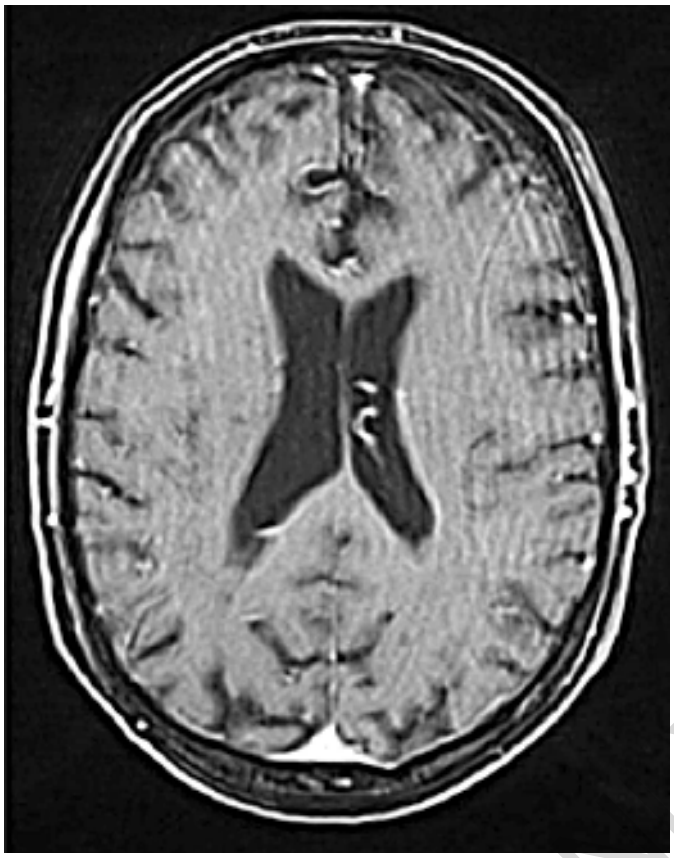

Fig: 8: Axial gadolinium contrast-enhanced T1-weighted MRI showing the complete disappearance of the right intra-axial frontal lobe lesion after two months since the tacrolimus discontinuation.

Discussion

Since tacrolimus is widely used in transplant patients and newer immunosuppressive drugs have not been developed, a better understanding of it and other existing agents is vital to improve patient outcome and prevent severe side effects. Tacrolimus inhibits calcineurin, a protein phosphatase required for T-lymphocyte activation, by binding FKBP-12, an immunophilin responsible for signal transduction that facilitates protein folding, intracellular transportation, and the stability of multiprotein complexes [19]. More specifically, tacrolimus forms a pentameric complex with Ca^{2+}, calmodulin, and calcineurin 1; the molecular structure of this complex blocks dephosphorylation of nuclear factor of activated T-cells (NFAT), a transcription factor needed for IL-2 expression, which leads to failure of T-cell clonal expansion [20].

Although tacrolimus is an effective immunosuppressant, significant adverse side effects are known. Tacrolimus-induced PRES was first described by Hinchey et al. [3] in a patient presenting with headache, seizures, and altered mental status. Clinical manifestations of PRES include non-specific symptoms such as headache, confusion and tremor, as well as severe ones, including impaired mental status, seizure, coma, and delirium [21].

Despite the implementation of molecular studies and modern advances on par with other fields within neurosurgery [22-40], the pathogenic mechanisms underlying neurotoxicity remain unclear [41]. Proposed mechanisms include cytotoxic edema after prolonged drug exposure and direct endothelial damage causing vasoconstriction and inhibition of the expression of drug-efflux pumps [16]. Moreover, it has been suggested that tacrolimus can cross the blood-brain barrier and attach to myelin, resulting in a direct toxic effect [42].

Subcortical white matter seems to be the component of the nervous system most involved in tacrolimus neurotoxicity, and clinical frames can vary, as the literature demonstrates. Absence of precise radiological correlates makes it difficult to identify tacrolimus-induced cerebral lesions. A study conducted by Furukawa et al. in 2000 reported 7 patients who underwent tacrolimus therapy after liver transplantation; all shared generalized seizures and disturbed consciousness as symptoms but MRI showed no typical pattern [43].

Furthermore, there appears to be no correlation between tacrolimus dosage or blood level and the onset of neurological symptoms, which manifest in an unpredictable fashion. Drug discontinuation has proven to be an effective strategy, given the subsequent disappearance or prompt reduction of neurological symptoms and radiological signs.

Tacrolimus-induced nervous system lesions and their histopathologic features remain poorly understood. However, biopsy appears to be a useful additional diagnostic tool to rule out tumoral, inflammatory, or infectious lesions and search for a possible tacrolimus-induced pattern. Stereotactic biopsy is a minimally invasive option which can allow accurate diagnosis and appropriate following treatment, on a par with other minimal invasive techniques, as reported by our group [44-59]. From this perspective, neurosurgery plays an important role in the management of patients with tacrolimus-induced neurotoxicity. However, further studies are warranted.

Conclusion

Neurotoxicity is an important and debilitating side effect of chronic use of tacrolimus after organs' transplantation. It can occur with various dosages and when the drug level is within normal range.

MRI is the preferred radiological imaging modality to detect tacrolimus-induced nervous system lesions, particularly T2 and FLAIR sequences. However, no typical pattern of pathology has been found.

Tacrolimus-induced neurotoxicity remains a diagnosis of exclusion and its features make it challenging to understand. Biopsy and histopathological study are imperative in order to rule out other pathology before discontinuing the drug.

Riassunto

Il Tacrolimus è comunemente usato per prevenire il rigetto dopo il trapianto di organi solidi e cellule staminali ematopoietiche. Nonostante la neurotossicità sia un noto effetto collaterale del farmaco, non vi sono quadri clinici, radiologici o istopatologici che siano patognomonici per una corretta diagnosi, che rimane al momento ancora sottostimata.
Lo scopo del presente studio è stato condurre una revisione omnicomprensiva della letteratura relativa alla neurotossicità indotta da tacrolimus in corso di terapia cronica immunosoppressiva secondaria a trapianti d'organo. Le manifestazioni cliniche e radiologiche di tale complicanza sono molteplici e si manifestano anche quando il farmaco è nel normale range terapeutico. Nella maggior parte dei casi la risonanza magnetica guida la diagnosi mostrando il coinvolgimento della sostanza bianca sottocorticale. Ai fini della diagnosi differenziale è importante anche la biopsia cerebrale, pur non mostrando quadri di specificità.
Una rapida e corretta diagnosi di neurotossicità indotta da tacrolimus è propedeutica alla sospensione del farmaco. Una conseguente regressione della sintomatologia, accompagnata dalla scomparsa delle lesioni, si verifica nella maggior parte dei casi.

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