ISSN: 2349-9141

Available online at http://www.ijirr.com

International Journal of Information Research and Review
Vol. 2, Issue, 04, pp. 584-588, April, 2015

OPEN ACCESS JOURNAL

Case Study

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME AND TOXOPLASMIC ENCEPHALITISIN HIV-INFECTED PATIENTS

[1]Ermira Muco, [1]Arjan Harxhi, [2]Arben Rroji, [2]Dorian Skenderaj, [1]Edmond Puca, [1]Elda Qyra, [3]Mario Pipero [1]Dhimiter Kraja, and [1,]*Pellumb Pipero

[1]Infectious Diseases Service, Outpatient Clinicof HIV/AIDSand Sexually Transmitted Diseases, UHC "Mother Teresa" Tirana, Albania
[2]Service of Imaging, UHC "Mother Teresa", Tirana, Albania
[3]Faculty of Public Health, University of Debrecen, Hungary

***Corresponding Author**

Received 25th March 2015; Accepted 30th April 2015

Abstract

Toxoplasmic encephalitis (TE) is one of the most frequent opportunistic infections in HIV/AIDS patient especially when CD4+ T lymphocyte are <100 cells/µL. Immune Reconstitution Inflammatory Syndrome (IRIS), also known as immune restoration disease, refers to a disease or pathogen-specific inflammatory response in HIV-infected patients that may be triggered after initiation or re-initiation of Highly Active Antiretroviral Therapy (HAART) or change to more active HAART therapy. IRIS is usually accompanied by an increase in CD4 cell count and/or a rapid decrease in viral load. We are presenting two cases with their clinical, imaging and laboratory findings, which are extracted from 23 patients with TE. Average time between beginning of ARV and the onset of IRIS was 35.5 days. Average value of CD4 cell count at presentation was 52cells/mm3 and CD4 cell in TE-IRIS was 140cells/mm3. Brain CT/MRI showed multiple lesions. Treatment withSulfamethoxazole/Trimethoprim resulted effective.

Keywords: Immune Reconstitution Inflammatory Syndrome, HIV, Toxoplasmosis, Albania.

To cite this paper: *Ermira Muco, Arjan Harxhi, Arben Rroji, Dorian Skenderaj,Edmond Puca, Elda Qyra, Mario Pipero Dhimiter Kraja, and Pellumb Pipero. 2015. Immune Reconstitution Inflammatory Syndrome and Toxoplasmic Encephalitisin HIV-Infected Patients. International Journal of Information Research and Review. Vol. 2, Issue, 04, pp. 584-588.*

INTRODUCTION

Toxoplasma gondii is a protozoan infectious disease with worldwide distribution. In fact *T gondii* is one of the most common causes of chronic infection with an intracellular organism in humans. A chronically infected individual who develops defects in cell-mediated immunity is at high risk for reactivation of the infection. The Toxoplasma Encephalitis (TE) is one of the most frequent opportunistic infections and as a consequence the most important cause of cerebral focal lesions in HIV/AIDS patients. (Osunkalu Vo, Akanmu Sa *et al.,* 2011; Nissapatorn *et al.,* 2004) Patients with CD4 cell counts below 200/mL, an antibody titer of ≥150 IU/mL was found to be predictive of toxoplasmic encephalitis. (Derouin 1996) IRIS (Immune reconstitution inflammatory syndrome) also known as immune restoration disease refers to a disease - or pathogen-specific inflammatory response in HIV-infected patients, that may be triggered after initiation or re-initiation of highly active antiretroviral therapy or change to more activeHAART therapy. The incidence of IRIS in patients initiating HAART is not well defined at present, with published estimates ranging from less than 10% to over 50%. (Bower *et al.,* 2005; Kumarasamy *et al.,* 2004; Narita *et al.,* 1998; Lawn *et al.,* 2005; Ortega-Larrocea *et al.,* 2005). TE occurring shortly after starting ART has been described, (Michelet *et al*., 1998; Tsambiras *et al.,* 2001; Pfeffer *et al.,* 2009; Tremont-Lukats *et al.,* 2009) However the risk of TE in HIV-infected persons decreased after the introduction of *Toxoplasma Gondii* prophylaxis and the use of HAART. (Pozio *et al.,* 2004 Antinorio *et al.,* 2004; Angel. Mayor *et al., Am J Trop Med May 2011*; Lewis John Haddow *et al.,* 2012)

Case Reports

Case one,

A 51 year-old man presented with three days history of high grade fever, severe headache, confusion, vomits, lethargy. He was diagnosed with HIV/AIDS infection earlier. He referred chronic diarrhea, weight loss, oral candidiasis, frequent allergic dermatitis. In base line examinations he had CD4+ T lymphocyte 80cells/µL/3.%; viral load was $9.55x10^3$. He was an emigrant. He was MSM (Table 1).

The chest X ray and ultrasound of the abdomen were normal. The head CT was normal (Fig1). There was no evidence of any other opportunistic infections.

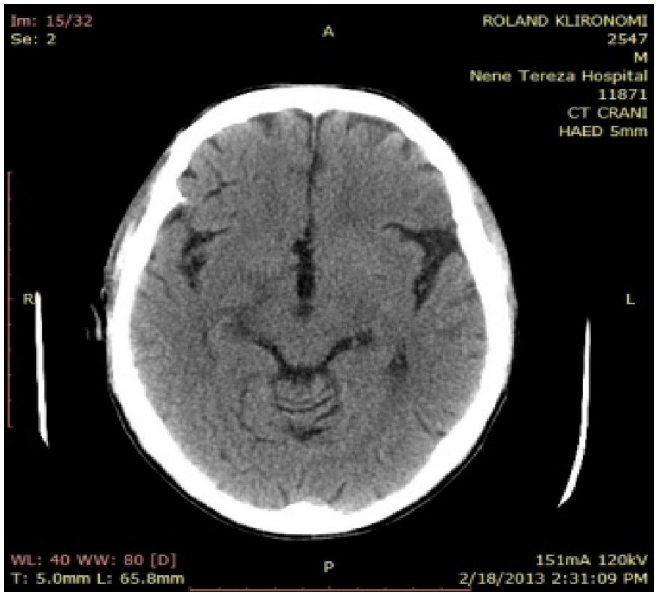

Fig. 1. Normal imaging of head CT

We starting treatment with normal HAART protocol (Tenofovir 300mg/day, Lamivudine 600mg/day, Efavirenz 600mg/day). In 33-day of HAART the patient presented with the clinical signs above. During objective examination he presented left hemiparesis, left facial paralyze andlight nucal rigidity. The CT of the head showed right peritalamichypodense ring lesion 6x4.7 cm localized near the right pedunculi, other lesions in right basal ganglions. Another sinister hypodense frontal periventricular lesion 3x3.6 cm. It is observed compression of the third and lateral ventricle due to edema and lateral displacement of median structures. (Fig 2)

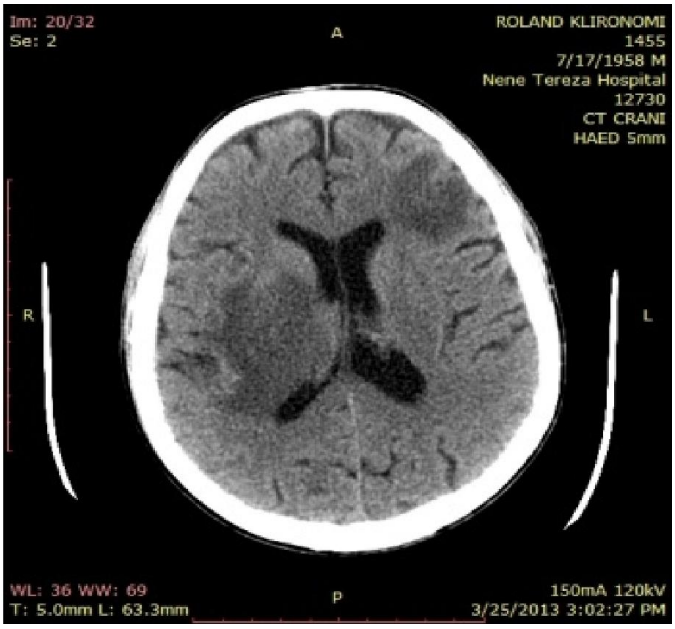

Fig. 2. Compression of the third and lateral ventricle and lateral displacement of median structures

Laboratory findings: CD4+ T lymphocyte 120cells/μL/19.%; Hg 9.7; Hct 31.1%; RBC 3.76M/uL; ELISA Toxo IgG antibodies 2239 UI/ml; HCV ab negative; HbsAg positive; CRP 38; γIFN negative; RPR negative, TPHA negative; ELISA CMV negative; ELISA HSV negative; ELISA EBV negative; hepatic and renal function was normal. The patient was treated with Sulfamethoxazole/Trimethoprim 1.92gr/pos three times daily;Deksamethasone 4mg/IV four times daily; Mannitol 100 ml/IV three times daily and the HAART. Despite the patient presented maculo-papuloz rush and abdominal pain, during the therapy, we did not interrupt the treatment with TMP-SMX. On the 4 day of the treatment we noticed the improvement of the left hand. On the 8 day of the treatment he moved the left leg. On the 13 day of the treatment the facial paralysis is visibly improved and the patient can move freely. Brain MRI after 35 days of therapy was really improved. He left hospital with HAART treatment and TMP: SMX 960mg/2tb/day.

Case two,

A 45 year-old man presented with a four-day history of severe headache, vomiting, fever and seizures. The patient was diagnosed with HIV/AIDS infection earlier and started HAART therapy 38 days ago.(Zidovudine 600mg/day; Lamivudine 300mg/day, Efavirenc 600mg/day) with very good adherence . By that time he complained wasting syndrome, oral candidiasis, seborroic dermatitis, frequent pneumonia and hemiparesis of the right arm during medical examination at present. In base line examinations we had CD4+ T lymphocyte 24cells/μL/1.9%; viral load was $3.45x10^5$copies/ml. There was no evidence of any other opportunistic infection. The patient was MSM (Table 1). Brain MRI imaging showed left subcortical lesion and left parietal lesion 6x4.5 cm with surrounding edema and hyper signal after iv contrast. (Fig 3,4)

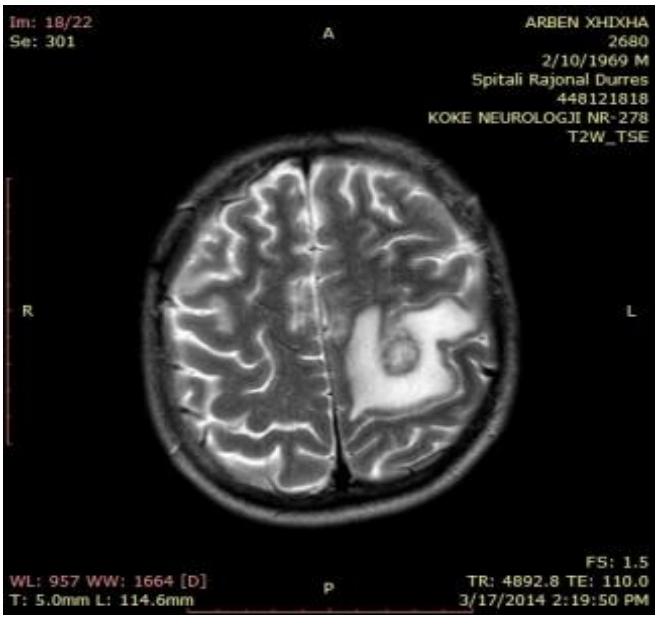

Fig. 3, Brain MRI left subcortical lesion and parietal lesion

Laboratory findings: CD4+ T lymphocyte 160cells/μL/5.1%;ELISA Toxo IgG antibodies 600 UI/ml; Hg 9.1; Hct 30.1%; RBC 3.46M/uL;γIFN negativ;

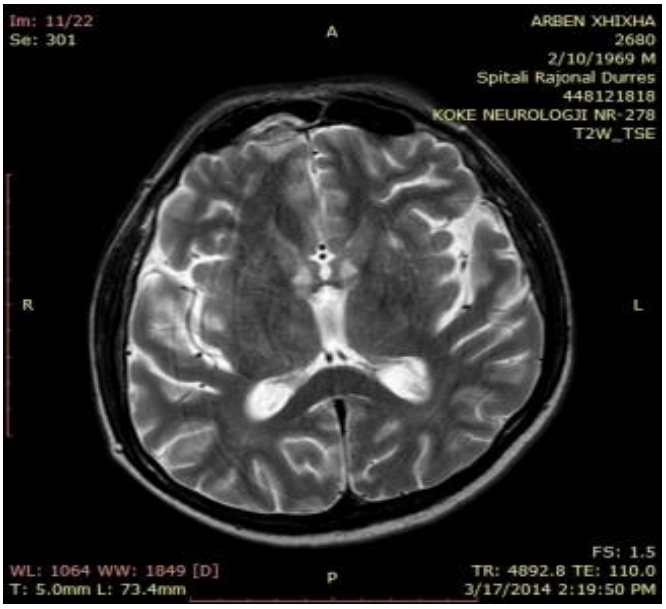

Fig.4,Brain MRI left subcortical lesion and parietallesion

RPR, TPHA negative; HCV ab negative; HbsAgnegative; ELISA CMV negative; ELISA HSV

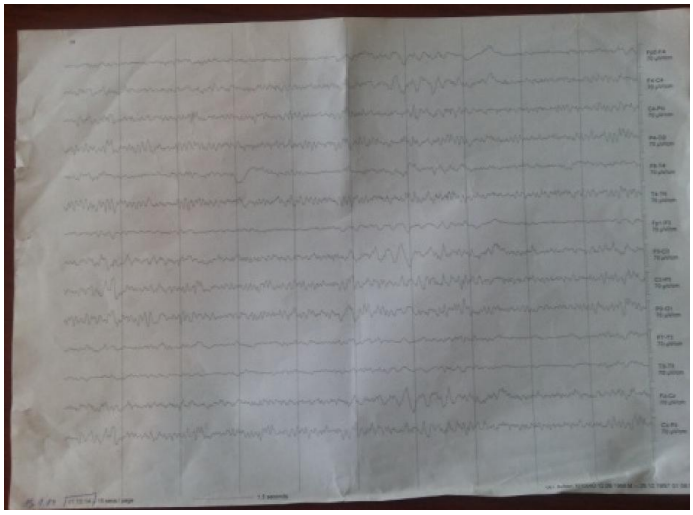

Fig 5. Epilepsy image of EEG

negative; ELISA EBV negative; CRP 46; Hepatic and renal function was normal.CT all body was normal; EEG gave us data on epilepsy (Fig 5). We started treatment with Sulfamethoxazole /Trimethoprim 2tb three times per day, (0,96gr) parenteral Deksamethasone 4mg four times per day,

Table 1. Epidemiological, Laboratory, Clinical characteristics of our cases with TE-IRIS.

Epidemiological, Laboratory, Clinical characteristics of our cases with TE-IRIS		Case 1	Case 2
Epidemiological Characteristics	Sex Age old Education Emigrated Married	Male. 51years old. High School Graduation. Yes. Homosexual	Male. 45years old. High School Graduation. Yes. Homosexual.
Clinical characteristics	HIV/AIDS defined illness in baseline.	Chronic diarrhea; Weight loss; Oral candidiasis	Wasting syndrome; Oral candidiasis; Seborroic Dermatitis; Frequent Pneumonia
	Signs and symptoms in TE-IRIS	Fever; Headache; Confusion; Vomits; Lethargy; Left hemiparesis; Left facial paralyze; Light neck rigidity.	Severe headache; Vomiting; Fever; Convulsions; Paresis of right arm.
	Interval between commencement of HAART and the onset of IRIS.	33 days.	38 days.
	HAART	Tenofovir; Lamivudine. Efavirenc.	Lamivudine; Efavirenc. Zidovudine.
	Full clinical improvement	After 13 days	After 11 days
LaboratoryCharacteristics	CD_4 count at beginning of HAART/ the median CD_4	80cells/µL(3.%)/ 52cells/µL (2.45%)	24cells/µL(1.9%)/ 52cells/µL (2.45%)
	CD_4 in TE-IRIS/ the median CD_4 Viral load at beginning of HAART.	120cells/µL(19%)/ 140cells/µL(12.05%) $9.55x10^3$ copies/mL	160cells/µL(5.1%)/ 140cells/µL(12.05%) $3.45x10^5$ copies/mL
	ELISA ToxoIgG-Ab	2239 UI/ml.	600 UI/ml
	Increase CD_4/ median increase	40cells/µL (16%)	136cells/µL (3.2%
	Immune status of spouses.	HIV1(+)	HIV1(-)
TreatmentCharacteristics	Etiological therapy	Baktrine/3x2tb0.96gr.	Baktrine/3x2tb0.96gr.
	Symptomatic therapy	Deksamethason/4x4mg Mannitol/3x75ml.	Deksamethason/4x4mg, Mannitol/3x75ml, Depakine/ 2x1tb0.5mg.

Mannitol 75ml three times per day, Depakine 0.5mg two times per day together with HAART. On the 5 day of therapy he is improved moving the arm up and down. On the eleventh day he had no more hemiparesis of the arm.Brain MRI after four weeks showed that subcortical lesion was disappeared and the parietal lesion was smaller 2.1x2 cm. (Fig 6, 7). In this conditions the patient was discharged with HAART and TMP-SMX 0.96mgx2/day.

DISCUSSION

This study describes two HIV infected persons in state of AIDS which showed Toxoplasmic Encephalitis of Immune Reconstitution Inflammatory Syndrome after Highly Active Antiretroviral Therapy. It still remainsan important problemthatbothersotherauthors too. (Angel Mayor *et al.2011,*; Lewis John Haddow, *et al.,* 2012). Two, out of 23 cases, in our study, presented TE-IRIS (8.69%). IRIS at our patients is presented like unmasking of subclinical disease. The patients starting HAART therapyinadvancedstageofimmunodeficiency which means that earlier diagnosis through active screening could help better treatment.

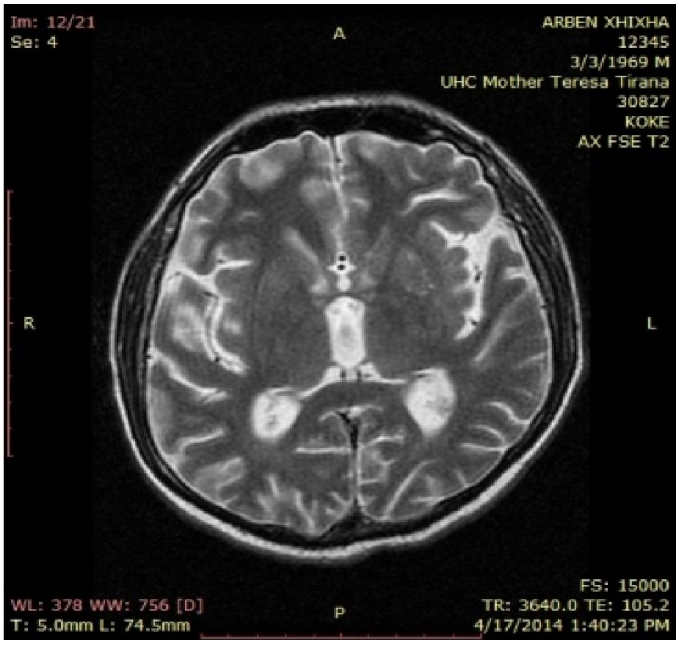

Fig 6. Imaging of brain MRI four weeks after treatment

The median CD4 count at beginning of HAART was 52cells/mm3. Lower CD4+ cell count at HAART initiation is the risk factor for the development of IRIS. (Braitstein *et al.,* 2006; Murdoch *et al.,* 2007) They were both men which is consider a risk factor for developing IRIS, (Murdoch *et al.,* 2007) the median age was 48 years and median interval between beginning of HAART and the onset of IRIS was 35.5 days, same as other authors consulting from us (Murdoch *et al.,* 2009; Emilio Letang *et al.,* 2011). The median CD4 in TE-IRIS was 140cells/mm3 with a median increase 88cells/mm3 from baseline screening. Clinical presentation was with signs and symptoms of an encephalitis including paresis too (Guillaume Martin-Blondel *et al*., 2011). Antibodies Toxoplasma IgG was positive in both cases. TMP/SMX is considering first line of treatment, well tolerated, with good results and cost effective (Guillaume Martin-Blondel*et al*., 2011; Guillaume Béraud *et al*., 2009). Our patients had good adherence for HAART but no TE prophylaxis, which is considering as a major factor for reducing relapse of the disease. In this context HIV-infected patients should be tested for *T. Gondii* antibodies (Kaplan*et al*., 2009).

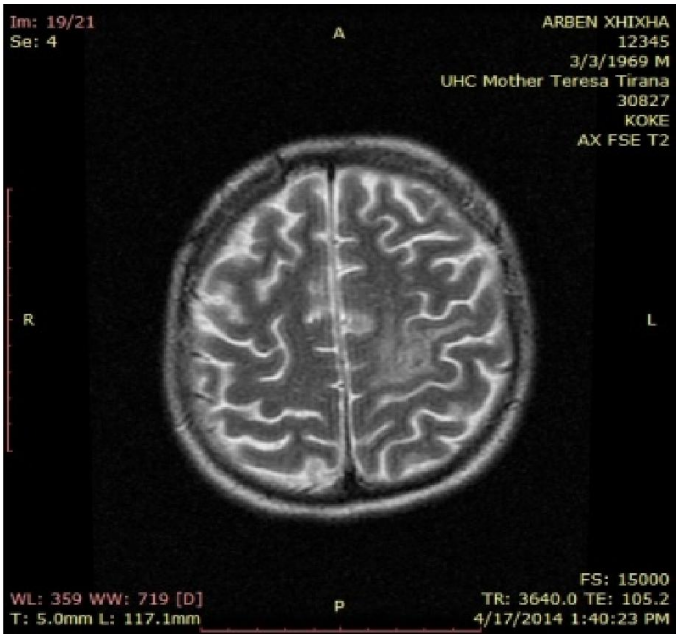

Fig 7. Imaging of brain MRI four weeks after treatment

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