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Case report

Acute leukocytosis during alemtuzumab treatment in patients with active relapsing-remitting multiple sclerosis

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ABSTRACT

Multiple Sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system and is one of the main causes of disability in young adults.

Alemtuzumab is a humanized monoclonal anti CD52 antibody approved for active relapsing-remitting (RR) multiple sclerosis (MS) exerting its strong clinical efficacy by a specific pattern of depletion of CD52-positive immune cells followed by their repopulation. As with most infused biological therapies, infusion-associated reaction (IAR) are frequently reported as adverse events for alemtuzumab treatment. In addition to cellular depletion, bystander effects including transient cell activation and triggered cytokine release are thought to cause alemtuzumab-specific IARs.

We describe acute laboratory changes during first alemtuzumab infusion week in a RRMS patient, underling acute changes in immunological and routine laboratory parameters.

1. Background

Alemtuzumab is a monoclonal antibody approved for treatment of adult RRMS patients that selectively bound to the CD52 protein, present on the surface of T and B cells and to a lesser extent on other cells. The treatment with alemtuzumab determines the depletion of circulating T and B cells, followed by a repopulation, which has different times for the different lymphocyte populations (Coles et al., 2012). Much immunological and clinical data are available regarding long-term follow-up after alemtuzumab treatment. Limited information is known about laboratory changes during the first alemtuzumab infusion week and pervious authors have already underlined the dramatic immunological effects of this drug due to cytokine release (Thomas et al., 2016).

We report a 33-year-old man with RRMS who presented an inadequate response to previous treatments with interferon and fingolimod. He also underwent to some non pharmacological treatment to manage his symptoms (Iodice et al., 2017, 2015).

At our last evaluation, patient had an EDSS 3.0 with clinical and radiological relapse. For this reason, we enrolled him to alemtuzumab treatment.

Although, our patient underwent premedication with corticosteroids (methylprednisolone 1 gr), antihistamines (ranitidine 50 mg and cetirizine 10 mg), paracetamol (1 gr) before infusion as suggested by the CARE-MS program to reduce the chances of IARs (Caon et al., 2015), the patient experienced an unusual infusion-associated (IAR) reaction related to alemtuzumab.

2. Case report

Immediately before the first infusion of a standard dose of alemtuzumab (12 mg/day for 5 days preceded by 1000 mg methylprednisolone, 10 mg cetirizine, ranitidine 50 mg, and 1000 mg paracetamol for three consecutive days), the patient showed normal hematobiochemical investigations.

Three hours later patient became sick with nausea and fever up to 40 °C not responsive to common anti-pyretic drugs.

Therefore, hematobiochemical investigations have showed lymphocytes below the detection limit but a sudden and marked neutrophilia with and a high increase of the not-specific indices of inflammation. In detail, blood results were the following: Hb 11.3 g/dl, RBC 6.08 × 10^6/µl, PLT 162.000/µl, WBC 16,740/µl with Neut 99.2% (16,610/µl), Linf 0.2% (30/µl). D-dimer 14.2 mg / l, Protein C Reactive (PCR) 4.1 mg/l, Procalcitonin Test (PCT) 7.1 ng/ml.

Six hours after the end of infusion, a further increase in leukocytosis was observed.

As he didn't have new neurological symptoms, brain imaging nor lumbar puncture were performed, but to rule out any infection conditions blood and urinary culture were performed with negative results.

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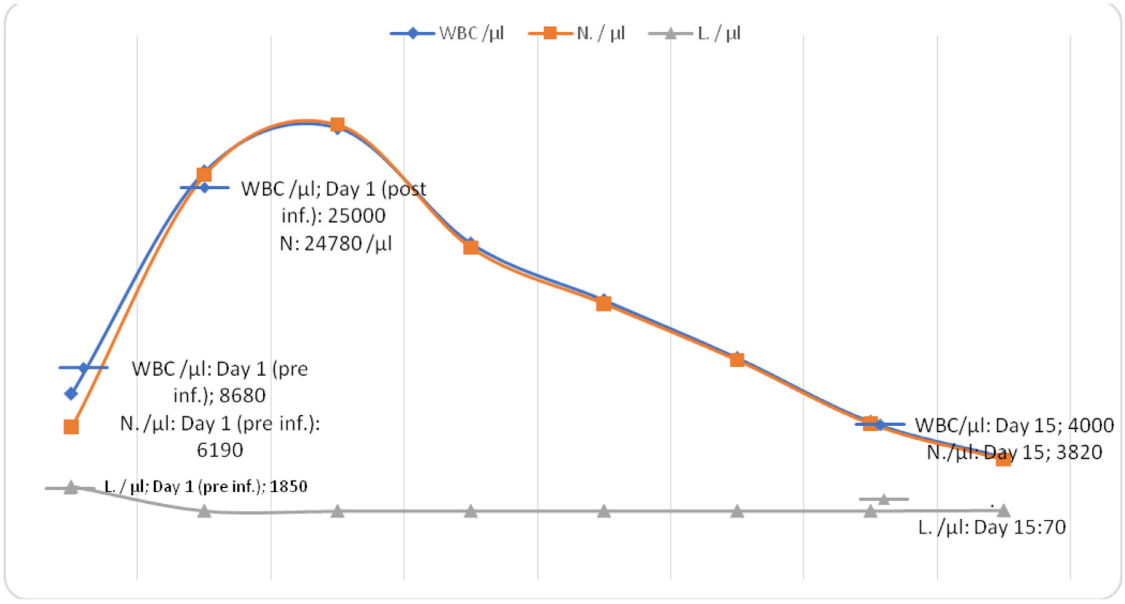
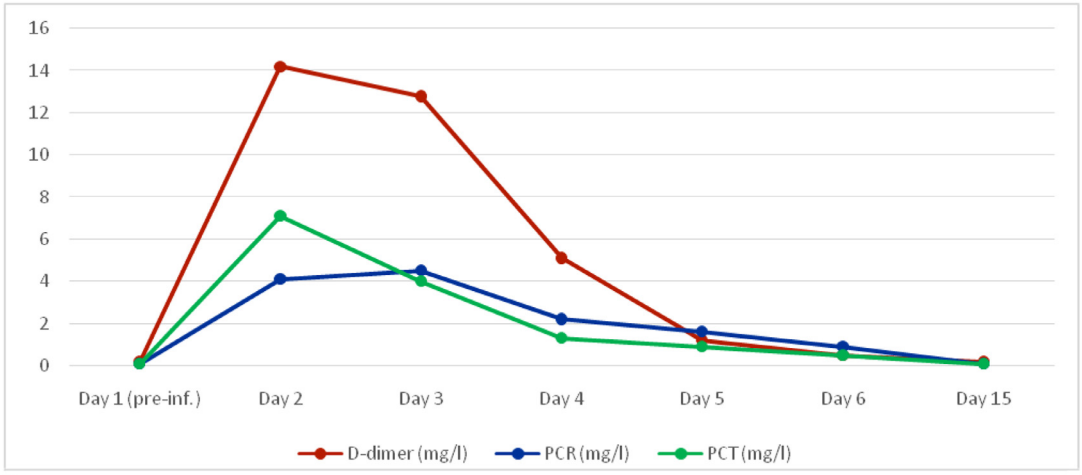


a



b

Fig. 1. a: leukocytosis is evident from the first day and is fully supported by the neutrophilic share. The title remains high until 48 h after the first infusion and then decreases until normalization on the sixth day. The lymphocyte title remains low until the last day.
Fig. 1b: rapid increase of the nonspecific indices of inflammation immediately following the infusion. Decrement of the values after 48 h the infusion with normalization after 5 days.

Despite the fact that the semeiological objectivity was negative, we have practiced lung tac because cryptococcosis, aspergillosis, fungal infections are fearsome complications that are poor in symptoms in the initial phase (Dubbioso et al., 2013; Henn et al., 2014). It was negative.

The administration of the alemtuzumab continued.

During following days, patient remained apiretic but neutrophilia grows up reaching the maximum value on the second day and then decreasing until normalization at the end of the alemtuzumab cycle (Fig. 1a/1b).

Two weeks after the end of the alemtuzumab infusion, all bloody and biochemical values remained in normal range. The follow-up run on the thirtieth day showed the persist reduction of the lymphocyte count and the normalization of all other values as know.

3. Discussion

The adverse effects of alemtuzumab reported in trials included potentially severe reactions to the infusion, as well as a risk of infections and cancer due to profound and prolonged immunosuppression. It's mechanism of action results in rapid lymphocyte depletion followed by slow repopulation. CD52-specific cell depletion is responsible for the high clinical efficacy as well as for IARs common with cell-depleting monoclonal antibodies. In our patient, after the first alemtuzumab infusion, granulocyte counts markedly increased, whereas lymphocyte counts dramatically decreased. Standardized infusion procedures including pretreatment management can attenuate immunological and clinical effects of alemtuzumab. Although our patient reported feeling well, C-reactive protein and procalcitonin peaked at serum levels consistent with septic condition but decreased during the following days. As previous reported, all these immunological effects can be due to lymphocytes destruction and cytokine mediated effects. Cytokine release syndrome is an adverse event that results in laboratory alterations similar to those found in the course of infection and infectious complications are the most feared adverse events in immunosuppressive treatments (Maggi et al., 2011; Moreau et al., 1996; Lee et al., 2014).

The management of this adverse event essentially goes from the clinical observation of the patient in which the clinical evidence must be to guide diagnostic-therapeutic pathways.

Our patient was subjected to all the screening and vaccinations indicated in the technical sheet with an extension of the same in order to avoid adverse events.

Limited informations are available regarding immunological and laboratory changes during the first week of alemtuzumab infusion. In clinical trials, laboratory tests were performed only before and 1 month after alemtuzumab infusion.

Because IARs can simulate infections, it is important to know the changes in classical laboratory parameters during alemtuzumab infusions. It could be useful to keep in mind the acute polymorphonuclear leukocytosis as a further acute reaction associated with the infusion in order to prevent misdiagnosis.

Thus we recommend clinicians be aware of clinical symptoms and vital data to initiate supportive analysis rather than standard laboratory testing within the first alemtuzumab week.

Disclosures

Authors reported no disclosures

Conflict of interest

All authors have contributed significantly, have read the paper and are in agreement with the content of the manuscript.

We confirm that the manuscript is not under simultaneous consideration by any other publication.

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