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Case Report

Multiple cranial nerve palsies revealing blast crisis in patient with chronic myeloid leukemia in the accelerated phase under nilotinib during severe infection with SARS-COV-19 virus: Case report and review of literature [☆]

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ABSTRACT

Since the introduction of tyrosine kinase inhibitors as primary therapy for patients with chronic myeloid leukemia (CML), the prognosis of these patients has improved significantly, and the number of patients who progress to the blast phase has decreased considerably. We report the case of a 35 year-old CML patient in accelerated phase treated with nilotinib, who presents a severe COVID-19 infection requiring non-invasive ventilation, and who subsequently presents a multiple cranial nerve palsy revealing a blast crisis of his CML. Multiple cranial nerve palsy is a sign of neurological involvement of CML in its blast phase. The blast crisis represents a real challenge for the clinician, especially during COVID-19 infection. The treatment remains the association of a tyrosine kinase inhibitors with a chemotherapy protocol, as well as the administration of methotrexate and cytarabine by intrathecal and intravenous infusion in high doses. Despite the importance of the association of CML with

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COVID-19 infection, there is not yet enough data to know the true impact of this infection on the evolution of this hemopathy.

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INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative disorder secondary to a translocation t (9;22) (q34;q11) known as Philadelphia chromosome, resulting in a BCR-ABL fusion gene. This results in an accumulation of myeloid cells in the bone marrow and the blood [1]. This disease can present in 3 phases depending on the blast rate: the chronic phase, the accelerated phase and the blast phase, the latter is known by its severity and its very high morbidity and mortality, but fortunately, few CML patients progress to this phase after the introduction of tyrosine kinase inhibitors (TKIs), and the prognosis has become almost the same in the general population for patients in chronic phase CML [2].

CASE PRESENTATION

We report the case of a 35 year-old CML patient in the accelerated phase on nilotinib with a last myelogram done one month before his admission showing 12% of blasts, admitted to the emergency room for a dyspnea dating back 2 days. On admission, the patient is conscious, with a GCS of, 15 of 15, dyspneic with a SpO₂ on room air of 87%, polypneic at 23 cpm without cyanosis, hemodynamically the patient is tachycardic at 123 cpm, with a normal blood pressure, and the temperature is 37.6°C. Weight is 92 kg with a height of 173 cm and a BMI of 30.73 kg /m². The clinical examination reveals an abdominal breathing. Given the pandemic context, COVID-19 RT-PCR test is performed and comes back positive. A non-contrast chest CT scan (Fig. 1) is performed and shows peripheral ground-glass lesions typical of SARS-CoV-2 infection, with pulmonary involvement estimated between 25%-50%. The patient is transferred to COVID-19 intensive care unit, and put on a high concentration oxygen mask with a flow rate of 15 per minute for a target SpO₂ between 90% and 92%.

Blood analysis shows high ferritinemia 7960 ng/ml (normal 30-300 ng/ml), high C-reactive protein 260 mg/l (normal 0-6 mg/l), D-Dimers 5 mg/l (normal 0-0.5 mg/l), Fibrinogen 9.3 g/l (normal 2-4 g/l), Lactate dehydrogenase 756 UI/l (normal 125-143 UI/l), the blood count was otherwise unremarkable.

The patient is put on the following therapeutic protocol: Vitamin C 2g/d, Zinc 45mg 1cp/12h, corticosteroid therapy with dexamethasone 6mg/d, therapeutic dosing of low-molecular-weight heparin (LMWH) 8000UI/12H and gastric protection with proton pump inhibitors (PPIs) 20mg/d, as well as his tyrosine kinase inhibitor nilotinib. The patient is stabilized and the evolution is favorable.

On day 2 of his admission, the patient presents greenish sputum with a fever of 38.7°C. White blood cell count is

12658/μl (Normal 4000-10000/μl), segmented neutrophils 9870 (Normal 1500-7000/μl). The patient is treated with antibiotic therapy based on ceftriaxone with levofloxacin. The evolution is favorable with clinical improvement and normalization of the infectious testing after 2 days.

On day 6 of his admission, the patient reports respiratory difficulties even under 15l per minute of oxygen with high concentration mask, and SpO₂ decreases to 85%. A chest CT scan without and with contrast injection is performed (Fig. 2) showing this time worsening of the lesions with a parenchymal involvement of more than 75%, without signs in favor of a pulmonary embolism. The patient is put on a non-invasive ventilation mode with an inspiratory positive airway pressure (IPAP) set at 10 mmhg, and a expiratory positive airway pressure (EPAP) at 7 mmhg, the patient is respiratory stabilized with a saturation at 92%.

On day 8, the patient is put on HFNC (high-flow nasal cannula) with a flow rate of 40l per minute and a FiO₂ of 50%, associated with 16 hours per day of prone position sessions, with a good improvement.

On day 14 of his hospitalization, the patient develops a right hemifacial deviation, ptosis, diplopia and dysphagia. A head CT scan with and without contrast injection (Fig. 3) is performed and comes back without particularities. A brain MRI (Magnetic resonance imaging) (Figs. 4, 5 and 6) shows abnormalities in the left cerebral peduncle, suggesting neuro-meningeal leukemia. Fig. 5

On day 15 the patient presents with profuse epistaxis with thrombocytopenia at 50,000/μl (Normal 150,000 - 400,000/μl) and normocytic normochromic anemia with hemoglobin at 8.9g/dl (Normal 12-16 g/l). Given his history of accelerated CML, a blast phase transformation of the CML is suspected, the decision is to perform a lumbar puncture and a myelogram. Anticoagulation is stopped given the risk of bleeding and resumed at a dose of 4000 IU/24h after 48 hours.

The myelogram shows 49% of blasts with immunophenotyping in favor of B-cell acute lymphoblastic leukemia (ALL) (ALL-L2 according to the French-American-British classification), and the lumbar puncture shows leukocytes at 2587 cells/μl (Normal less than 10/μl) with a negative bacteriologic examination and positive blast detection.

The decision is to put the patient on the HYPER-CVAD chemotherapy protocol in association with nilotinib, and intrathecal chemotherapy based on methotrexate and cytarabine for the neuro-meningeal involvement.

On the respiratory level, the evolution is favorable with a switch to oxygen therapy using only nasal cannula with a flow of 5l per minute after 34 days of his admission. Hematologically, the patient regressed the cytopenias, and improved clinically with a total regression of the cranial nerve palsy.

About 37 days after admission, the patient is transferred to the hematology department with a very good evolution.

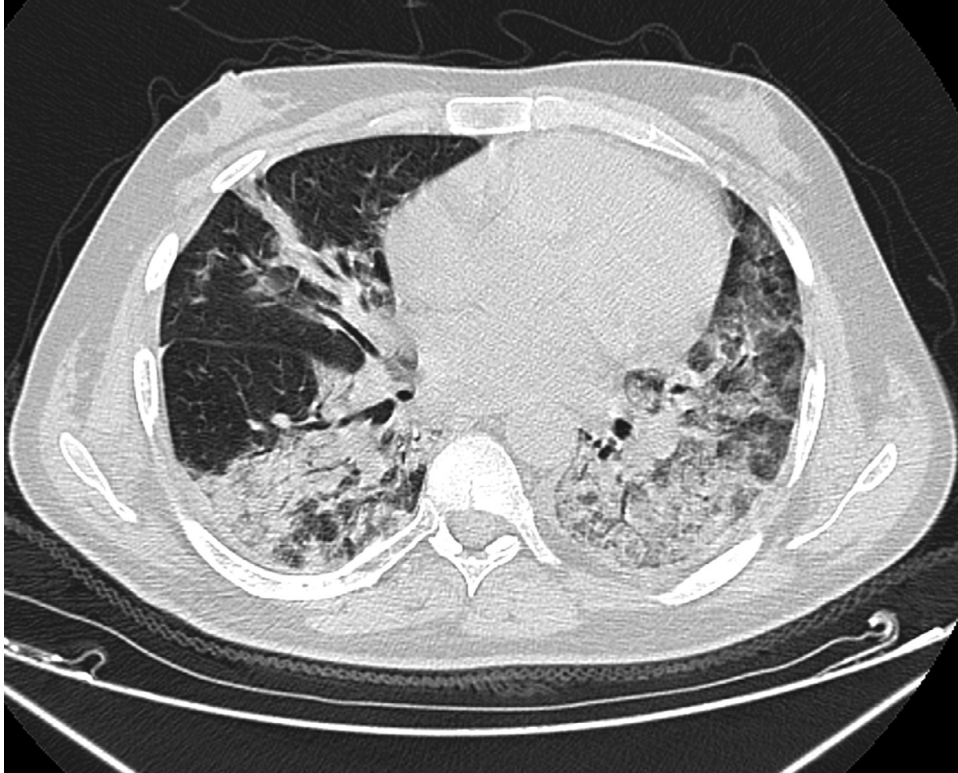


Fig. 1 – Axial nonenhanced chest CT image (lung window) showing bilateral ground-glass opacities typical of SARS-COV 19 infection with pulmonary involvement estimated between 25% and 50%

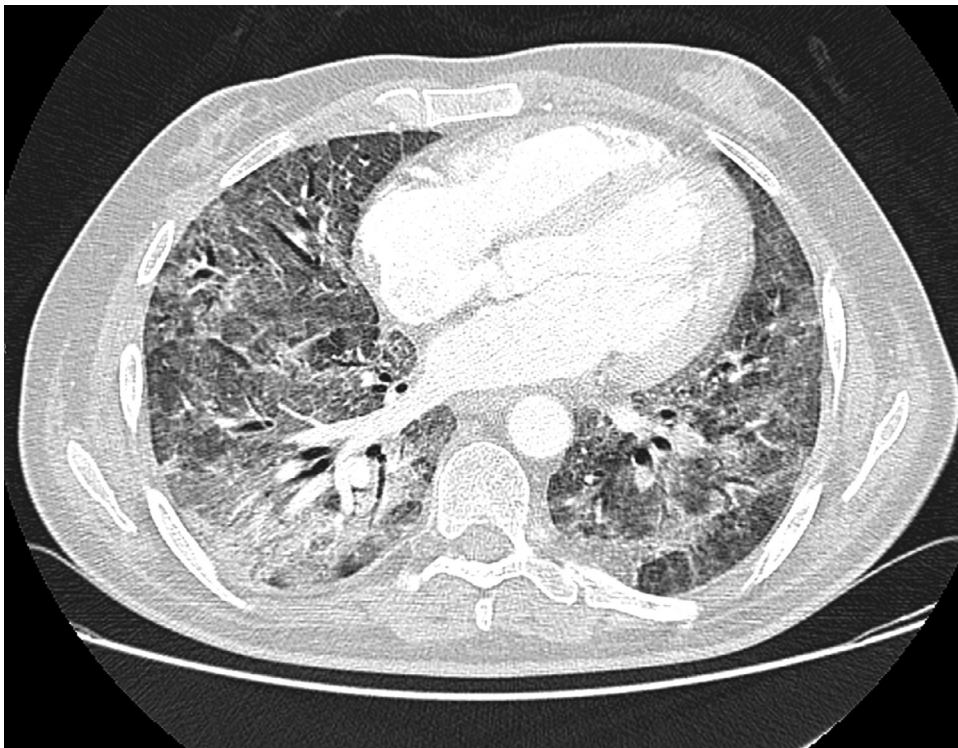


Fig. 2 – Axial Contrast-enhanced chest CT image (lung window) showing worsening of the lesions with an estimated pulmonary involvement of more than 75%



Fig. 3 – Head CT scan with and without contrast injection showing no abnormalities

DISCUSSION

In December 2019, in Wuhan, China, the world experienced the appearance of a virus, which has caused millions of cases of severe acute respiratory syndrome, it is the new corona virus SARS-COV-2 [3]. A few months later, the virus had spread all around the world, sending the world into a state of sanitary alert requiring a total confinement after that the World Health Organization declared the infection a pandemic in March 2020 [3].

SARS-COV-2 belongs to the beta coronavirus family (β -CoVs), it mainly uses the angiotensin-converting enzyme receptor 2 (ACE2) to enter cells, this receptor is expressed mainly in the lungs, which explains the pulmonary tropism of the virus [4]. The source of the virus is currently the patients infected with the virus, and patients with severe disease are considered more contagious than others [4]. The virus is primarily transmitted between people through direct contact with respiratory droplets [3].

The severity of the infection is mainly explained by the inflammatory storm secondary to the overexpression of inter-

leukine 6 and the hypercoagulable state secondary to the overexpression of tissue factor and the inflammatory storm at the same time [4].

After 18 months from the beginning of the pandemic, the management of patients with CML on TKIs remains a challenge for clinicians given the lack of sufficient studies concerning the clinical, epidemiological and therapeutic characteristics as well as the evolution of these patients [5]. Despite the immunosuppression secondary to the leukemia itself and to the immunosuppressive treatments [6], some authors suggest that these patients could have a good prognosis thanks to a reduced inflammatory response [6].

Li et al. were the first to report the characteristics of Covid-19 infection in CML patients, the prevalence was 9 times higher than the general population, but without clinical severity or increase in the mortality rate compared to the general population [[5],[6]], but it remains a very small sample to determine the real prevalence.

According to Li et al. almost half of the CML patients diagnosed with COVID-19 infection were in the accelerated or blast phase, and the treatment was mostly imatinib, but none of them were on a second-generation TKI [7].

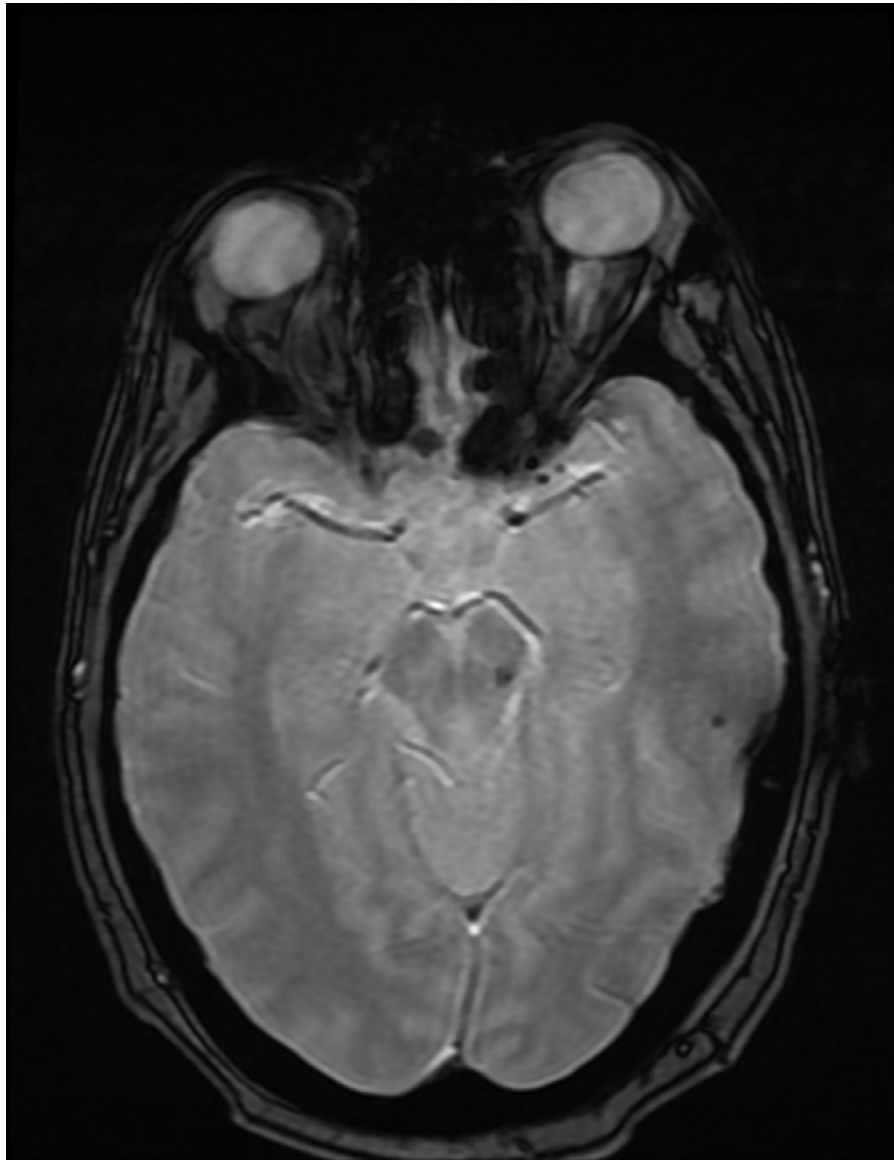


Fig. 4 – T2*-weighted imaging MRI sequence of the brain showing a hypointense area in the left cerebral peduncle

According to a study conducted by Semih et al. to follow the evolution of CML patients under a TKI during COVID-19 infection, these patients had a very good outcome, a low mortality rate and thus few severe cases compared to the control group, but all results were without statistical significance [8]. In the same study, there was no difference in terms of severity or mortality between the use of imatinib or nilotinib during SARS-COV-2 infection, but the sample size remains very small to generalize these results [8].

According to the International Blood and Marrow Transplant Registry, the blast phase is defined by a blast percentage higher than 30% in the peripheral blood or in the bone marrow [9]. It should be noted that the prognosis of CML patients has completely changed after the introduction of TKIs, and the proportion of patients diagnosed in the accelerated

phase or the blast crisis phase does not exceed 5% [9]. Patients in the blast phase have a poor prognosis, given the high risk of infection and bleeding, and their management remains difficult, especially since these patients are resistant to TKIs [9].

Multiple cranial nerve palsy is a rare neurological complication of the blast phase of CML, and is secondary to either hyperviscosity or direct infiltration of nerves by blasts [10]. Another hypothesis for this neurological involvement is the poor diffusion of the therapies used in the central nervous system (CNS) [11].

The cerebrospinal fluid (CSF) study looks for blasts, and the molecular study can detect the BCR-ABL oncogene which is pathognomonic of CML [12]. But imaging remains an essential diagnostic tool, especially cerebral MRI since it is more

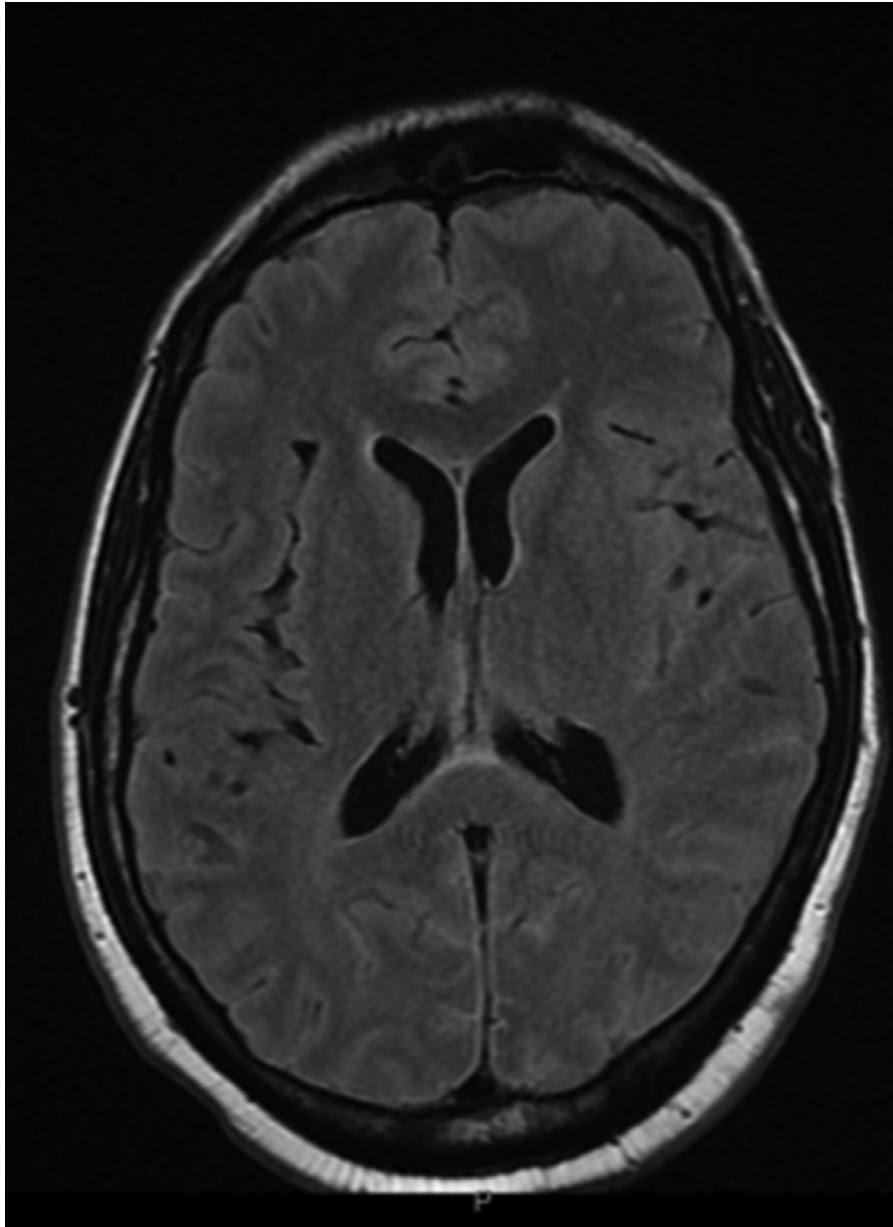


Fig. 5 – T2 FLAIR brain MRI sequence showing hyperintense periventricular lesions

sensitive than CSF biology, and makes it possible to eliminate differential diagnoses [11].

The management of CML patients in chronic phase during COVID-19 infection is based on TKIs associated with the COVID-19 protocol. It should be noted that imatinib has shown its efficacy against SARS-COV and MERS-COV, and nilotinib against SARS-COV [8]. These data suggest the efficacy this therapeutic class against SARS-COV-2, but to date there is not enough data to discuss this hypothesis.

For CML patients who present with a blast phase transformation during COVID-19 infection, several protocols are proposed, citing the combination of a TKI, preferably ponatinib, with blinatumomab [13]. According to the European Working Group on Adult ALL, we can use the combination of a TKI with the HCVAD chemotherapy protocol [13], and the treatment of CNS involvement remains methotrexate with or without cytarabine intrathecally, generally associated with high sys-

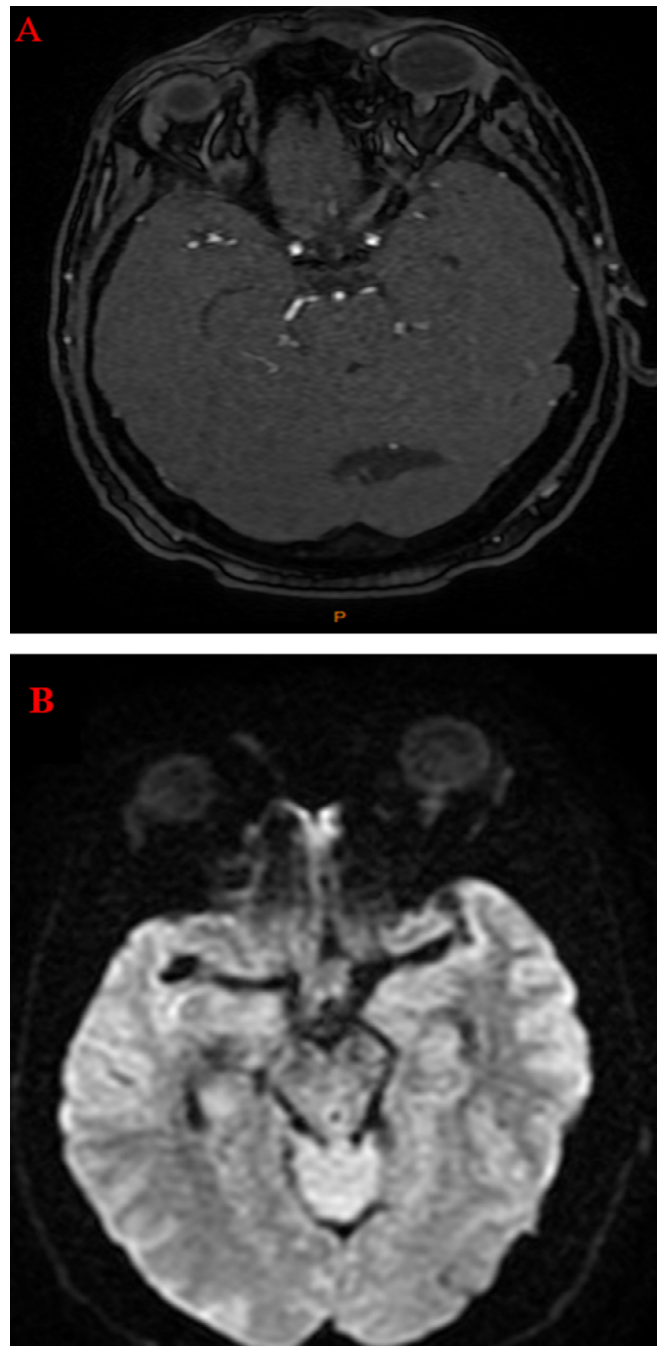


Fig. 6 – (A) 3D time-of-flight MRA sequence without abnormalities; (B) Diffusion-weighted imaging showing no abnormalities

temic dose of methotrexate with or without cytarabine [14].

CONCLUSION

Multiple cranial nerve palsy remains a rare sign which can reveal the transformation of CML into the blast phase, which is

known to have a very high mortality rate, yet our patient had a favorable outcome with a total recovery from the palsy and from the COVID-19 infection.

Patient consent

Obtained

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