NEUROLOGICAL COMPLICATIONS IN HEMATOLOGICAL DISEASES (PART ONE)

I. MYELOPROLIFERATIVE DISEASES (MPDS)

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ABSTRACT

The neurological complications are frequent in patients with hematological syndromes such as: myeloproliferative diseases, malignant diseases of lymphoid cells, plasmocytic diseases, transfusion biology and therapy, bone marrow and stem cell transplantation, disorders of the platelet and vessel wall, disorders of coagulation and thrombosis, hypoproliferative anemias, hemoglobinopathies, megaloblastic anemias, hemolytic anemias and acute blood loss, aplastic anemia, myelodysplasia and related bone marrow syndrome.
We proposed a synthetic review in two parts of the neurological complications in hemato-oncologic diseases that are present not only in relation with hematological disease itself, but in relation with systemic and intrathecal chemotherapy, radiotherapy and stem cell transplantation during the course and follow-up of the hemato-oncologic patient.

Key words: neurological complications, myeloproliferative disorders (MPDs), polycythemia vera (PV), essential thrombocytosis (ET), idiopathic myelofibrosis (agnogenic myeloid metaplasia – AMM), chronic myeloid leukemia (CML), acute myeloid leukemia (AL).

Under the umbrella of chronic myeloproliferative disorders (MPDs) generally are listed four well-recognized entities: (1) polycythemia vera (PV), (2) essential thrombocythemia (ET), (3) idiopathic myelofibrosis, which also is known as agnogenic myeloid metaplasia (AMM), and (4) chronic myelogenous/myeloid leukemia (CML). CML is quite distinct because of the presence of the Philadelphia chromosome which is associated with the *bcr/abl* gene rearrangement. This gene rearrangement is associated with an unfavorable prognosis, with transformation to a fatal, acute leukemia after a median of 3 to 4 years. The other three diseases are closely related and, on the whole, have a much more favorable prognosis. It is common for patients with PV to have incompletely expressed disease, so differential diagnosis with the other MPDs, particularly ET, may be difficult. Furthermore, as time passes, both PV and ET may evolve so that the clinical picture is indistinguishable from that of AMM. When the preceding illness was PV, such patients are referred to as having postpolycythemic myeloid metaplasia (PPMM) to distinguish them from patients with no prior hematologic disease. Because of these close inter-relationships, PV, ET, and AMM are best discussed together.

Polycythemia vera, essential thrombocytosis, idiopathic myelofibrosis and chronic myeloid leukemia are commonly classified together under the rubric the chronic myeloproliferative disorders, because their pathophysiology involves the clonal expansion of a multipotent hematopoietic progenitor cell with the overproduction of one or more of the formed elements of the blood. These entities may transform into acute leukemia naturally or as a consequence of mutagenic treatment.

I.A. POLYCYTHEMIA VERA

Polycythemia vera is a clonal disorder involving a multipotent hematopoietic progenitor cell in which

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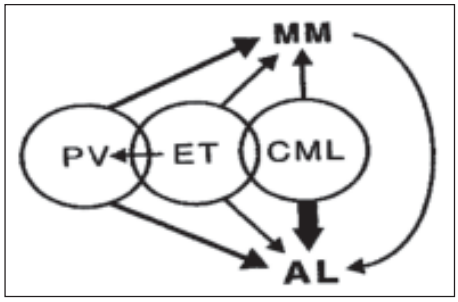

Figure 1. *Overlap and transitions in myeloproliferative disorders (MPD). Arrows indicate transitions that may occur, with frequencies suggested by the thickness of the arrows. In some patients with chronic myelogenous leukemia (CML), the presenting clinical picture may be very similar to that of essential thrombocythemia (ET). A minority of patients who present with ET will develop an increased red cell mass and, therefore, polycythemia vera (PV) over time. Almost all patients with CML will eventually transform to acute leukemia (AL), whereas only a tiny fraction of patients with PV or ET will do so unless they are put at greater risk by therapy with radiation or alkylating agents. A significant minority of patients with PV, ET, or CML will develop the clinical picture of myeloid metaplasia (MM). (from Murphy)*

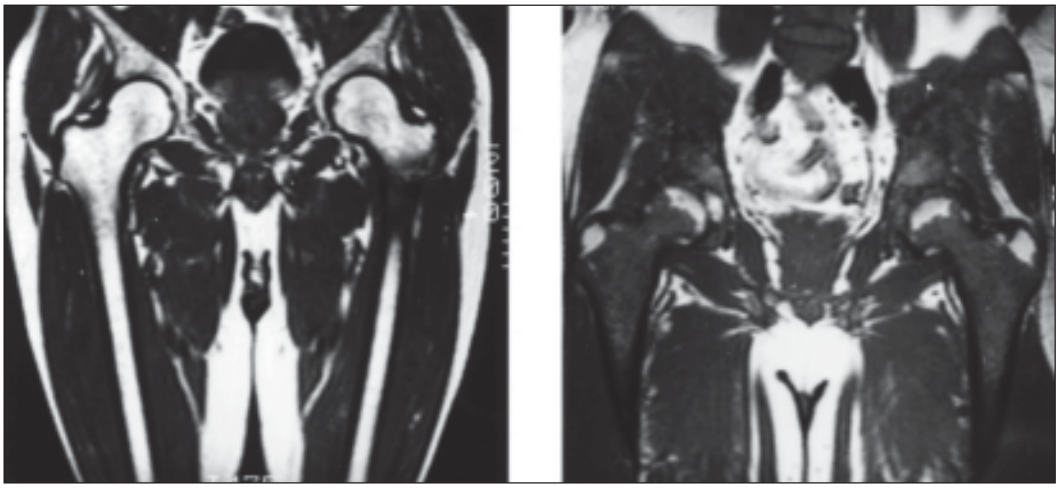

Figure 2. *Magnetic resonance images of the bone marrow in polycythemia vera (PV). In T1-weighted images, fatty and cellular marrow appear white and dark, respectively. Upper left, anormal fatty pattern for a 70-year old man with recently diagnosed PV. Upper right, a more advanced patient with densely cellular upper femoral marrow; however, the femoral head and greater trochanter have not yet reconverted to cellular marrow. (from Murphy)*

there is accumulation of phenotypically normal red cells, granulocytes and platelets in the absence of a recognizable physiologic stimulus.

Polycythemia vera, the most common of the chronic myeloproliferative disorders, occurs in about 2 per 100,000 people. Vertical transmission has been documented, establishing a genetic basis for the disorder.

The major clinical complications of polycythemia vera relate directly to the increase in blood viscosity associated with elevation of the red cell mass and indirectly to the increased turnover of red cells, leukocytes and platelets and the attendant increase in uric acid and histamine production

Neurologic manifestations occur frequently in polycytemia vera. Cerebral symptoms have been reported in from 5.6 percent to 78 percent of patients with this disease. One of the most common is intravascular thrombosis. In proportion of 32-38% the patients with polycytemia vera had cerebral thrombosis during the course of the disease. Erythrocytosis can lead to intravascular thrombosis involving small vessels of the brain and to clinical presentation of lacunar infarcts (Gruppo Italiano Studio Policitemia, 1995). Uncontrolled erythrocytosis can lead to various neurological symptoms such as vertigo, tinnitus, headache and visual disturbances.

Periodic phlebotomy serves to reduce hyperviscosity by bringing the red cell mass into the normal range. Low-dose aspirin is useful in patients with polycythemia vera and cerebral ischemic events in order to prevent arterial thrombosis. Oral anticoagulants are not routinely indicated with the exception of venou thrombosis.

Actual recommendations for management of polycythemia vera:

- Venesection to maintain the Hct to < 45%.
- Aspirin 75 mg/d unless contraindicated.
- Cytoreduction should be considered if:
  - poor tolerance of venesection;
  - symptomatic or progressive splenomegaly;
  - other evidence of disease progression, e.g. weight loss, night sweats;
  - thrombocytosis.

- Choice of cytoreductive therapy, if indicated:
  - < 40 years old: first line interferon, second line hydroxycarbamide or anagrelide;
  - 40–75 years old: first line hydroxycarbamide, second line interferon or anagrelide;
  - >75 years old: first line hydroxycarbamide, second line 32P or intermittent low dose busulphan.

Grade C recommendation: Evidence level IV.

Thromboembolic events in polycythemia vera

The European Collaboration on Low-dose Aspirin in Polycythemia vera (ECLAP) study established the therapeutic benefit of aspirin in polycytemia vera (Landolfi et al, 2004), and followed an earlier pilot study (Gruppo Italiano Studio Policitemia, 1997). Patients were randomised between aspirin 100 mg/d and placebo. Aspirin significantly reduced the risk of the combined end-point of non-fatal thromboembolic events, or death from cardiovascular causes. The risk of major or minor thrombosis was also significantly decreased. There was no significant increase in haemorrhage. The results of this large, well-designed multicentre trial eliminated the concerns about the efficacy and safety of aspirin that were raised by the earlier, smaller PVSG-05 trial (Tartaglia et al, 1986) and provided evidence for the use of aspirin in the management of polycytemia vera.

Conventional risk factors for atherosclerosis, including hyperlipidaemia and hypertension, have been assessed in myeloproliferative disorders with variable results. Little work has specifically been performed in polycythemia vera. Recent recommendations for the management of atherosclerosis would suggest that this patient group would benefit from aggressive risk management with the use of antihypertensives to maintain normal blood pressure and the use of a statin. An increased prevalence of antiphospholipid syndrome (APL) has been described in essential thrombocytosis and associated with increased risk of thrombosis (Harrison, 2002). There have been no reports thus far in this field for patients with polycytemia vera. Patients with persistent antiphospholipid antibodies should be managed according to guidelines for this condition (Greaves et al, 2000).

Recommendations for assessing risk of thrombosis for patients with polycytemia vera

- Patients should be screened for hypertension, hyperlipidaemia, diabetes and a smoking history taken.
- Conventional risk factors for atherosclerosis should be managed aggressively. All patients should be requested to stop smoking.
- No current evidence to support routine thrombophilia screening in polycytemia vera.

Grade C recommendation: Evidence level IV.

Haemorrhage in polycytemia vera

Haemorrhage is both a less frequent and generally less severe clinical complication of polycytemia vera than thrombosis. The principal sites affected are skin, mucous membranes and gastrointestinal tract. Haemorrhage is often reported in association with high platelet counts, acquired von Willebrand disease (Budde et al, 1984) and

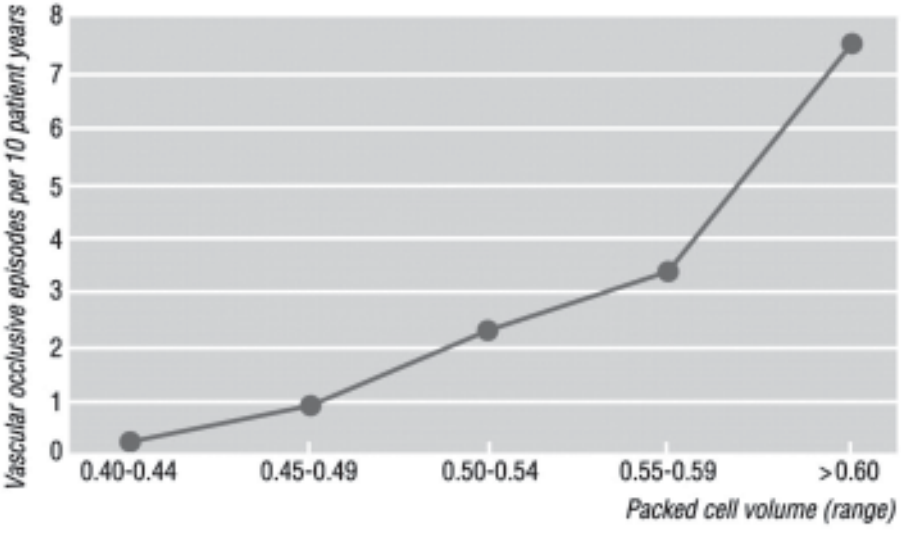

Figure 3. *Packed cell volume versus incidence of thrombotic events in patients with polycytemia vera*

high doses of anti-platelet therapy (Tartaglia et al, 1986). Low dose aspirin is infrequently associated with haemorrhagic complications (Landolfi et al, 2004). A wide variety of platelet function defects are reported in polycytemia vera but they are not predictive of bleeding.

Extramedullary hematopoiesis in polycytemia vera

Extramedullary hematopoiesis occurs in patients with various hematologic disorders involving a chronic increase in the production of red blood cells, and is often associated with thalassemia, but is less common in polycytemia vera. The most frequent sites are spleen, liver, and kidney. Extramedullary hematopoietic tissue occurring within the spinal canal and causing cord compression is very rare. Total surgical excision is not usually feasible because of the diffuse nature of extramedullary hematopoietic tissue and the possibility of reccurence, but acute neurologic deterioration does require emergency surgery. Extramedullary hematopoiesis is radiosensitive and displays a rapid response to low dosages, so radiation therapy is recommended for residual tumors. Considering the possibility of central nervous system extramedullary hematopoiesis in patients with polycytemia vera, an early diagnosis is necessary for a favorable prognosis.

I.B ESSENTIAL THROMBOCYTOSIS

Essential thrombocytosis is a clonal disorder of unknown etiology involving a multipotent hematopoietic progenitor cell and is manifested clinically by the overproduction of platelets without a definable cause. The essential thrombocytosis can occur at any age in adults and often occurs without symptoms or disturbances of hemostasis.

Characteristic platelet function abnormalities associated with essential thrombocytosis are not defined, and no platelet function test predicts the presence of clinically significant bleeding or thrombosis.

The actual suggested criteria for the clinical diagnosis of essential thrombocytosis are: platelet count > 500,000/microL, absence of a known cause of reactive thrombocytosis (hyposplenism, postsplenectomy, malignancy, collagen vascular disease, infection, hemmorhage, myelodysplasia, postsurgery, iron deficiency anemia), normal red cell mass, splenomegaly, absence of myelofibrosis, presence of marrow iron.

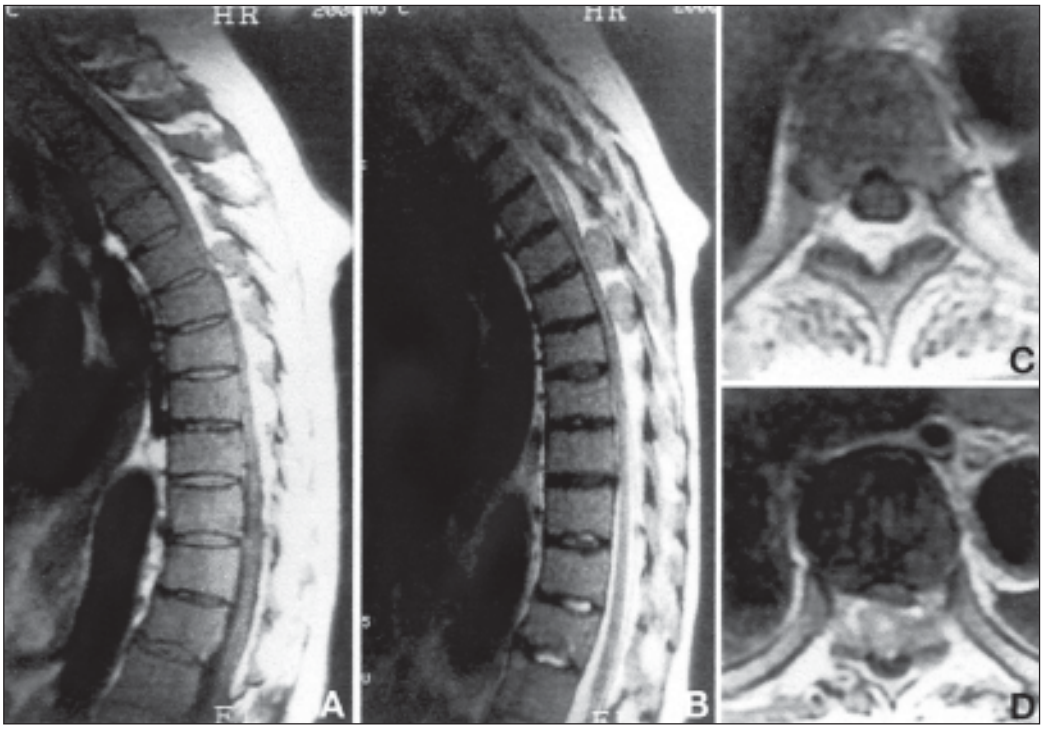

Figure 4. *A: T_1-weighted magnetic resonance image showing multiple extradural masses, extending from T-2 to T-9, isointense to the spinal cord. In particular, large posterior epidural masses are present from T-4 to T-8, compressing the cord. Note the thinning of the thoracic spinal cord on the sagittal view. B: T_2-weighted magnetic resonance image showing the epidural masses as mixed intensity. C, D: Axial T_1-weighted magnetic resonance images (C: T4-5 intervertebral level, D: T6-7 intervertebral level) showing heterogeneous enhancement after gadolinium administration. (after Ohta)*

It is commonly believed that a high platelet count (>1,000,000/microL) must cause intravascular stasis and thrombosis; on the contrary, very high platelets counts are associated primarily with hemmorhage (including cerebral), while platelets counts of <1,000,000/microL are more often associated with thrombosis (ischemic stroke attributed to essential thrombocythemia was found in 0.4% of cases, as reported in the Lausanne Stroke Registry).

The essential thrombocythemia may cause endothelial dysfunction and predispose to vascular damage such as carotid artery dissection.

One of the most important neurologic problems in essential thrombocytosis are migraine-related but may respond only to lowering of the platelet count and the other neurologic complications may represent an interaction between an atherosclerotic vascular system and a high platelet count. If platelet reduction is deemed necessary on the basis of neurologic symptoms refractory to salicylates, interferon-alfa or anagrelide (a quinazoline derivative) can reduce the platelet count.

One recent study published the prevalence of neurological abnormalities in patients with essential thrombocytosis and has attempt to identify risk factors for neurological complications. Ninety-five patient charts were reviewed from January 1983-July 1999. Seventy patients fulfilled the Polycythemia Vera Study Group criteria for diagnosing essential thrombocytosis. Eighteen patients (25.7%) had episodes of neurological impairment, 52 (74.3%) had none. Neurological features: cerebrovascular event – 9; chronic headache – 3 and dizziness – 3, mononeuritis multiplex, sinus vein thrombosis and epilepsy – 1 each. The interval between diagnosis of essential thrombocytosis and occurrence of neurological events ranged from time of presentation (10 patients) to 13 years (1 patient) with a high predominance of females, 88.8% and 55%, respectively. This study conclusion was that neurological complications occurred at presentation or during follow-up in approximately 25% of patients with essential thrombocytosis.

The principal causes of death in patients with essential thrombocythemia are thrombosis, hemorrhage, and progression to myelofibrosis or acute myelogenous leukemia. The myelosuppressive therapy that prevents vascular events in essential thrombocythemia may itself increase the risk of transformation to myelofibrosis or acute myelogenous leukemia. The challenge in treating essential thrombocythemia is to prevent bleeding and thrombosis without increasing this risk.

A risk-adapted treatment strategy can help physicians to meet this challenge. The important risk factors for thrombotic events in patients with essential thrombocythemia are an age of 60 years or more and previous vascular episodes, whereas hemorrhagic complications are paradoxically associated with extreme thrombocythemia. Young, asymptomatic patients with a platelet count of less than 1.5 million per cubic millimeter should be considered at low risk for thrombosis and hemorrhagic events, and do not require myelosuppressive treatment. By contrast, patients who are at least 60 years of age or who have a history of serious bleeding or thrombosis or a platelet count of 1.5 million per cubic millimeter or more should receive cytoreductive treatment. Hypertension, dyslipidemia, diabetes, and smoking can also increase the risk of thrombosis; patients with these coexisting conditions may constitute an "intermediate risk" category, but the assignment of patients to this subgroup is not universally accepted.

The myelosuppressive agent of choice in patients who have essential thrombocythemia and a high risk of thrombosis is hydroxyurea. This drug was found to be effective in reducing the incidence of thrombosis in a trial that randomly assigned 114 high-risk patients to receive either hydroxyurea or no cytoreductive therapy. After a median follow-up of 27 months, thrombosis developed in 3.6% of the treated patients, whereas 24% of the untreated patients had one or more thrombotic events. The major concern regarding hydroxyurea is whether it is leukemogenic. However, to date, no randomized studies with sufficient statistical power have been conducted to determine whether the risk of leukemia in patients treated with hydroxyurea is higher than the inherent risk that essential thrombocythemia will evolve into acute myelogenous leukemia. Nevertheless, the putative risk of leukemia associated with hydroxyurea prompted investigators to test new drugs that lack this potential, such as anagrelide and interferon alfa.

The hypothesis raised by De Stefano's data concerning a limited efficacy of chemotherapy in patients with previous cerebrovascular event does not seem confirmed by the findings of the PT1 trial which indicated that, in aspirin-treated patients, hydroxyurea provides greater protection than anagrelide against cerebrovascular events (fig.5). We should be aware of the limitations of these comparisons which include limited numbers of events and differences in both study design and outcome measures. However, since there is no

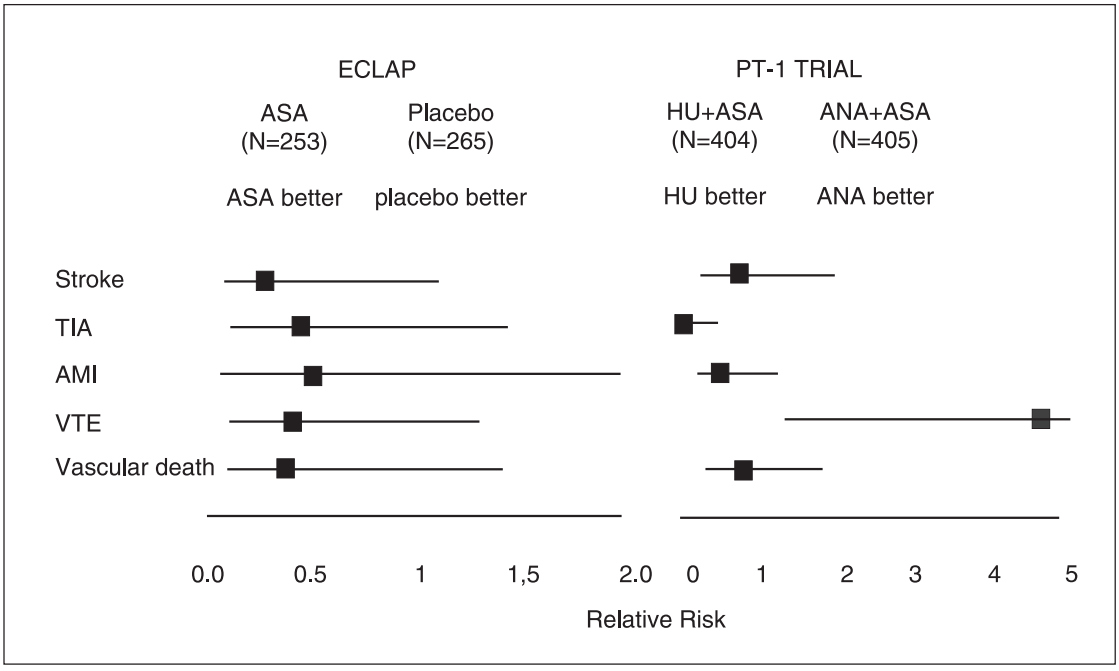

Figure 5. *Point estimates and confidence intervals of relative risks for different vascular events in patients randomized in the ECLAP[1] and PT-1 trial.[27] N: number of patients; ASA: aspirin; HU: hydroxyurea; ANA: anagrelide; TIA: transient ischemic attack; AMI: acute myocardial infarction; VTE: venous thromboembolism.*

convincing evidence of a differential efficacy of aspirin and hydroxyurea in the various arterial districts, both patients with previous stroke or transient ischemic attacks and those with previous myocardial infarction should be treated with these two agents with a possible indication for more aggressive use of hydroxyurea in subjects with previous myocardial infarction and persistent leukocytosis. Patients with venous thrombosis are best treated with short-term anticoagulation, which may be more prolonged when thrombosis manifests at unusual sites, followed by long-term use of hydroxyurea and aspirin.

Recommendations for management of patients with essential thrombocythemia (ET):

1. All patients:
– manage reversible cardiovascular risk factors aggressively (e. g., smoking, hypertension, hypercholesterolemia, obesity)
2. High-risk patients (prior thrombosis or age > 60 years or platelets > 1,500,000/microL)
– low-dose aspirin plus hydroxyureea (anagrelide or interferon-alfa second line)
3. Intermediate-risk patients (age 40-60 years, no high-risk features)
– either enter into randomized trial
– or low-dose aspirin (consider cytoreduction if other cardiovascular risk factors present)
4. Low-risk patients (age <40 years and no risk features)
– low-dose aspirin

I.C IDIOPATHIC MYELOFIBROSIS (PRIMARY)

Idiopathic myelofibrosis is a clonal disorder of a multipotent hematopoietic progenitor cell of unknown etiology. In contrast to the other chronic myeloproliferative disorders, which can occur at any age, idiopathic myelofibrosis primarily afflicts individuals in their sixth decade or later.

The main features are bone marrow fibrosis, extramedullary haemopoiesis (that is, production of blood cells within organs such as the spleen), splenomegaly, and leucoerythroblastic blood picture (immature red and white cells in the peripheral blood). Good evidence exists that the fibroblast proliferation is secondary (reactive) and not part of the clonal process. Idiopathic myelofibrosis needs to be distinguished from causes of secondary myelofibrosis.

Idiopathic myelofibrosis (primary) may have been present for many years before diagnosis. Patients could have had previous undiagnosed

primary polycythaemia or thrombocythaemia. The absence of an easily palpable spleen is rare. The main presenting features are abdominal mass (splenomegaly), weight loss (hypermetabolic state), anaemia, fatigue, and bleeding. Exuberant extramedullary hematopoiesis can cause ascites, pulmonary hipertension, pericardial tamponade, intracranial hypertension, spinal cord compression.

I.D. CHRONIC MYELOID LEUKEMIA

The incidence of chronic myeloid leukemia is 1.3/100,000 people per year. The incidence of chronic myeloid leukemia increases slowly with age until the middle forties when it starts to rise rapidly.

The diagnosis of chronic myeloid leukemia is established by identifying a clonal expansion of a hematopoietic stem cell possessing a reciprocal translocation between chromosome 9 and 22. The cytogenetic hallmark was recognized by the presence of a shortened chromosome 22 (22q-), designed as the Philadelphia chromosome.

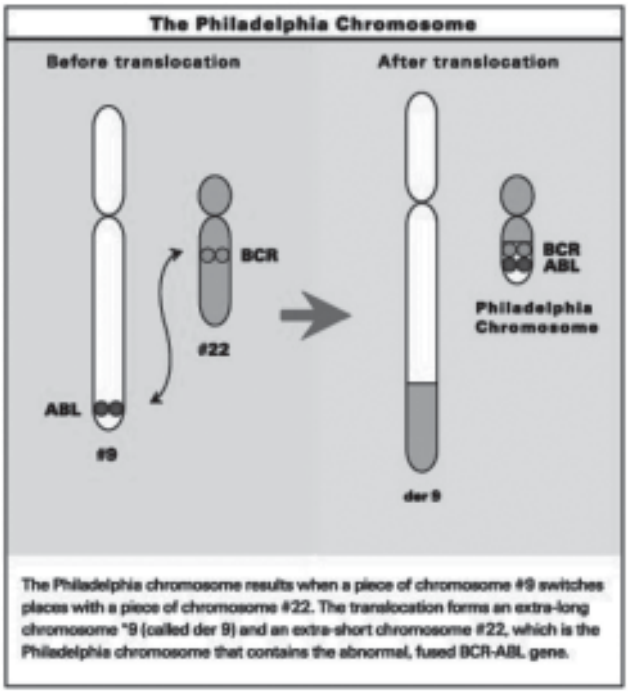

Figure 6. *The Philadelphia chromosome*

Elevated white blood cell counts, with various degrees of immaturity of the granulocytic series are present at diagnosis. Untreated, the disease is characterized by the inevitable transition from a chronic phase to an accelerated phase and on to blast crisis. The events associated with to the acute phase are poorly understood.

The clinical onset of the chronic phase is generally insidious – some patients present with fatigue, malaise and weight loss or have symptoms resulting from splenic enlargement. Less common are features related to granulocyte or platelet dysfunction, such as infections, thrombosis or bleeding. Occasionally, patients present with leukostatic manifestations due to severe leukocitosis or thrombosis such as vascular occlusive disease, cerebral ischemic events, venous thrombosis, visual disturbances.

One recent study published the results of neurological complications in patients with chronic myeloid leukemia. Using patients' case folders and haematological malignancy register all cases of chronic myeloid leukaemia seen in an University Hospital between July 1995 and June 2005 were retrospectively studied. All the available literature on the subject was also reviewed. Thirty-three cases of chronic myeloid leukemia were seen within the study period. Five (15.15%) of them had one or more sensori-neural defects. Of the five, two (40%) patients presented with bilateral hearing impairment, each beginning with the left ear; one (20%) presented with left ear hearing loss; one (20%) came with severe left ear tinnitus; one (20%) presented with complete bilateral hearing and bilateral visual losses. Fundoscopy showed leukaemic deposits on the retina. While the complications due to hyperleucocytosis-induced stasis recover following the conventional treatment, those due to other pathogenetic mechanisms such as leukaemic deposits do not return to their pre-morbid states following disease control despite the use of the currently available treatment protocols.

The goal of therapy in chronic myeloid leukemia is to achieve prolonged, durable, nonneoplastic, nonclonal hematopoiesis which entails the eradication of any residual cells containing the transcript. The therapy includes: allogeneic stem cells transplant, interferon-alfa, chemotherapy, autologous stem cells transplant, intensive leukapheresis (useful in emergencies where leukostasis related complications such as ischemic stroke are likely) and splenectomy.

Allogeneic hematopoietic stem cell transplantation (HSCT) is an excellent therapy option for a variety of serious malignant and benign diseases, including leukemias and myelodysplastic syndromes. There is, however, a relatively high incidence of transplant-related mortality (TRM) associated with complications arising from the procedure, which can be as high as 20 to 50%. The

main risk factors identified were the main risk status of the underlying disease, mismatched transplantation, previous diagnosis of advanced acute myeloid leukemia (AML), older age and the presence of grade II or higher graft-versus-host-disease (GVHD). Neurological complications of HSCT have been reported to occur in 2.8 to 70% of patients in different series. Usually, neurological complications of HSCT are caused by several factors, which include pretransplant chemotherapy and/or radiotherapy, conditioning regimens used, infections caused by the transplant-related immune deficiency and adverse effects caused by the drugs used either to prevent or treat GVHD.

Intracranial hemorrhage – particularly intracerebral hemorrhage – was the most common complication observed. In 2002 Bleggi-Torres et al. examined the results of 58 autopsies of patients who had received HSCT and had developed intracranial hemorrhage. The authors reported that 40 patients had intracerebral hemorrhage, 35 subarachnoid hemorrhage and eight subdural hemorrhage. In 16 cases bleeding was extensive and directly related to death. Intracerebral hemorrhage usually has a different evolution from that caused by systemic arterial hypertension, which is usually monophasic. Intracerebral hemorrhage observed in HSCT patients secondary to severe thrombocytopenia can have a slow but progressive clinical evolution because of the increase in the size of the hematoma, followed by mass effect, intracranial hypertension and transtentorial herniation. Difficulties with platelet replacement, persistent thrombocytopenia and problems recommending surgery because of the condition of the patients frequently cause intracranial hypertension with herniation refractory to treatment followed by brain death.

It is interesting to note that intracranial hemorrhages were more frequent (29% of cases) than brain infarctions in this series, a finding that differs from those reported in the literature. Davis and Patchell describe a similar incidence of brain infarction and intracerebral hemorrhage in patients who received HSCT. Another interesting aspect of reports in the literature is that the presence of brain infarction is generally related to infectious endocarditis or even marantic endocarditis.

Coplin et al, evaluated the incidence, etiology and prognosis of strokes in patients after HSCT. Of 1,245 patients who received HSCT, 2.9% had stroke, of which the most common causes were intracerebral hemorrhage related to thrombocytopenia (38.9% of cases) and the presence of brain infarction and hemorrhage secondary to fungal infection (20% of cases).

CNS bacterial infection is estimated to be present in between 1.3 and 5.3 % of cases. Among the most common causes of bacterial meningitis are *Listeria monocytogenes, Streptococcus pneumoniae, Klebsiella pneumoniae, Escherichia coli* and *Alpha streptococcus*.

Brandi et al., in a study of 865 HSCT patients, identified the infections that were found most frequently in HSCT patients. In their series neurological complications were observed in 27.6% of the cases, and 9.4% of the cases were caused by infection. Of all the cases with infections, 70.7% were due to infection of the peripheral nervous system caused by the Varicella-zoster virus, with intercostal radiculopathy, and 29.2% to infection of the CNS caused by various infectious agents. The most common of these were fungal (Aspergillus) and viral infections and toxoplasmosis encephalitis, followed by abscesses of different etiologies, and neurocysticercosis. A total of 53.6% of the patients had graft-versus-host disease.

Among the encephalitis, the most common etiologies are viral (herpes virus, cytomegalovirus and varicella-zoster virus) and fungal infections caused by *Aspergillus sp*. Medeiros et al. investigated the main CNS infections that occur after HSCT in an autopsy study of 27 cases. They found encephalic infections in 15% of the cases and fungal infections, particularly those caused by *Aspergillus sp,* followed by *Candida sp* and species of Fusarium, in 60% of the cases. *Toxoplama gondii* encephalitis was found in 8 cases and bacterial abscesses in 2% of the cases.

Jantunem et al. studied diagnostic aspects of invasive infections caused by Aspergillus in patients who received HSCT. They concluded that the lungs were the most commonly affected organs (90% of cases), followed by the CNS (41%). Thus, methods for early detection of fungal infections are extremely important for early diagnosis of this condition, and patients suspected of having this type of infection should start anti-fungal therapy at the same time as the diagnostic process is under way.

Human herpesvirus type 6 (HHV-6) infections are emphasized in the literature as being an important cause of viral encephalitis in HSCT patients. HHV-6 is a neurotropic virus, which often leads to a picture of encephalitis, particularly in immunocompromised hosts, such as HSCT patients. The diagnosis of encephalitis caused by

HHV-6 has become easier because PCR techniques can now be used in CSF.

Diagnosis of toxoplasmosis in patients submitted to HSCT was not common until some years ago, and its low prevalence in these patients compared with that in other immunocompromised patients (e.g., those with AIDS) was the subject of much debate. However, in the series published by Maschke et al, investigated the presence of opportunistic infection in 655 patients after HSCT, and 4% of the patients were found to have infections, and 74% of these had toxoplasmosis encephalitis. Denier et al. found CNS infections in 4.2 % of their cases, with a predominance of toxoplasmosis (1.4% of cases).

Wernicke encephalopathy is a neurological complication to which little importance is attributed in the international literature regarding neurological complications after HSCT. Majolino et al. reported the case of a patient who had a clinical picture compatible with Wernicke encephalopathy after the use of busulfan. The authors questioned the involvement of busulfan in the causality of thiamin deficiency.

Posterior reversible leukoencephalopathy (PRL) has been described in patients with renal insufficiency, patients with eclampsia, and patients with hypertensive encephalopathy; in the hematological patient, PRL is possibly related to the cytotoxic effects of drugs such as cyclosporine used as immunosuppressive therapy. In 2001, Teive et al reported eight patients who had received cyclosporine after HSCT and developed RPL.

Peripheral neurological system complications are generally less frequent after HSCT. There have been reports of cases of peripheral neuropathy secondary to chemotherapy, radiculopathy secondary to varicello-zoster virus infections and myositis related to chronic GVHD.

In 1997 Zétola described the pre- and post-HSCT neurological evaluation of 43 patients using clinical neurological exams and nerve conduction studies. The objective of the study was to investigate the possibility of peripheral nerve damage as a result of conditioning and immunoprophylaxis regimens used for HSCT (busulfan, cyclophosphamide, cyclosporine and methotrexate). However, the author failed to find any evidence that these drugs were toxic to the PNS in the patients studied.

More recently, a case of a patient with chronic inflammatory demyelinating polyradiculoneuropathy in chronic graft-versus-host disease following allogeneic hematopoietic stem cell transplantation was reported.

I.E ACUTE MYELOID LEUKEMIA

The incidence of acute myeloid leukemia is approximately 2.3 per 100,000 people per year, and the age-adjusted incidence is higher in men than in women (2.9 versus 1.9).

The categorization of acute myeloid leukemia into biologically distinct group is based on morphology, cytochemistry and immunophenotype as well as cytogenetic and molecular techniques.

The diagnosis of acute myeloid leukemia is established by the presence of >20% myeloblasts in blood and/or bone marrow. Acute myeloid leukemia is classified based on morphology and cytochemistry according to the French, American and British (FAB) schema which includes eight major subtypes.

FAB classification:

M0: Minimally differentiated leukemia
M1: Myeloblastic leukemia without maturation
M2: Myeloblastic leukemia with maturation
M3: Hypergranular promyelocytic leukemia
M4E0: Variant: Increase in abnormal marrow eosinophils
M4: Myelomonocytic leukemia
M5: Monocytic leukemia
M6: Erythroleukemia (DiGuglielmo's disease)
M7: Megakaryoblastic leukemia

The phenotype of myeloid leukemia cells can be studied by multiparameter flow cytometry after the cells are labeled with monoclonal antibodies to cell-surface antigens. Chromosomal analysis of the leukemic cell provide the most important pre-treatment prognostic information in acute myeloid leukemia.

Patients with acute myeloid leukemia most often present with non-specific symptoms that begin gradually or abruptly and are the consequence of anemia, leukocytosis, leucopenia or leukocyte dysfunction or thrombocytopenia. Half mention fatigue as the first symtom and anorexia and weight loss are common complaints. On occasion bone pain, lymphadenopathy, vision changes, headache or other non-focal neurologic abnormalities could be the first sign or symptom. Significant gastrointestinal bleeding, intrapulmonary hemorrhage, retinal or intracranial hemorrhage occur most often in M3 AML, but also in M5 AML. Infiltration of the gingivae, skin, soft tissue or the meninge with

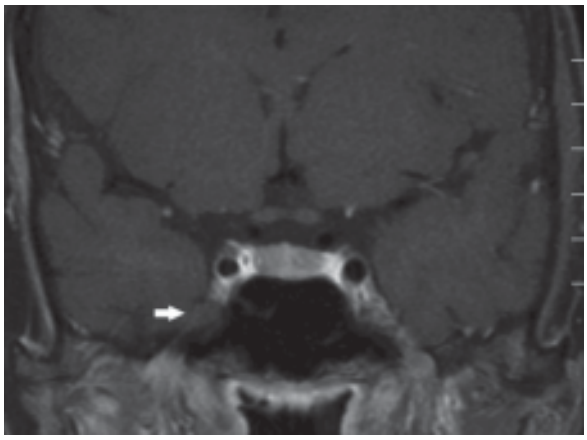

Figure 7. *The chloroma of mandibular branch (V3) of trigeminal nerve. Coronal contrast-enhanced T1-weighted MR image shows altered signal intensity of Meckel's cave (arrow) and right mandibular nerve in continuation throughout foramen ovale caused by chloroma. Trigeminal nerve was only site of involvement in this patient who complained of neuralgia.*

leukemic blasts at diagnostic is characteristic of the monocytic subtypes – M4 and M5 AML.

Rarely patients may present with symptoms from a mass lesion located in the soft tissues, cranial or spinal dura, bone or other organs. The mass lesion represents a tumor of leukemic cells and is called a granulocytic sarcoma or chloroma.

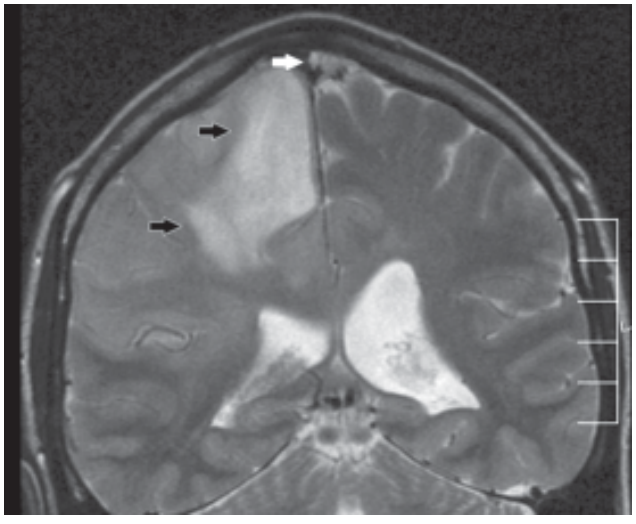

Figure 8. *The pachymeningeal chloroma – T2-weighted coronal MR image shows small left parasagittal meningeal mass near superior sagittal venous sinus (white arrow) showing T2 hyperintensity. In addition, there is right hemispheric glioma (black arrows) with large perifocal edema and compression of right lateral ventricle.*

Leukemia affects both the central, and peripheral nervous systems. Neurological complications are a consequence of both direct leukemic infiltration, as occurs with leukemic meningitis, and complications of either antileukemic treatment (e.g., thrombocytopenic or DIC-related intracranial hemorrhage, steroid myopathy, vinca alkaloid peripheral neuropathy, posterior reversible encephalopathy syndrome, multifocal necrotizing leuko-encephalopathy) or immune compromise (e.g., Herpes zoster or Aspergillus infection).

The manner in which leukemic cells enter the CNS is a subject of controversy, but the likely sources include hematogenous spread or direct spread from adjacent infiltrated bone marrow. Meningeal involvement is more common in the acute leukemias and may occur as part of the original presentation. More commonly however, meningeal spread occurs in the form of relapse after initial remission, despite aggressive anti-CNS prophylaxis. In addition to the morbidity and mortality associated with CNS relapse, the greatest risk is the invariable development of bone marrow/systemic recurrence which follows CNS relapse.

Leukemic meningitis may be diffuse or focal. The diagnosis of leukemic meningitis generally depends on the detection of leukemic cells in the CSF, however cytology can be falsely negative. Imaging may be necessary. Findings include hydrocephalus (may be the only finding), or an abnormal MR appearance of CSF on precontrast imaging. If CSF is not of appropriate signal intensity on T1 and T2-weighted images, the possibility of leukemic meningitis should be raised. Abnormal meningeal enhancement, in the cisterns or along the pial surface of the brain or spinal cord, is the surest sign of leukemic meningitis. This may be smooth or nodular. MRI is known to be far more sensitive in the detection of leptomeningeal tumor spread than CT, however CT can make this diagnosis in flagrant cases. Dural spread of leukemia is best detected radiologically as abnormally thickened and brightly enhancing dura on Gd-enhanced MRI.

Axial contrast enhanced MR image shows focal subarachnoid leukemic deposits (arrows). Areas of more generalized meningeal disease could be seen at other levels. Focal deposits such as these in the subarachnoid space are not as common as more diffuse meningeal disease, and if unaccompanied by other areas of more generalized involvement, may be difficult to differentiate from focal dural leukemic masses or even parenchymal disease.

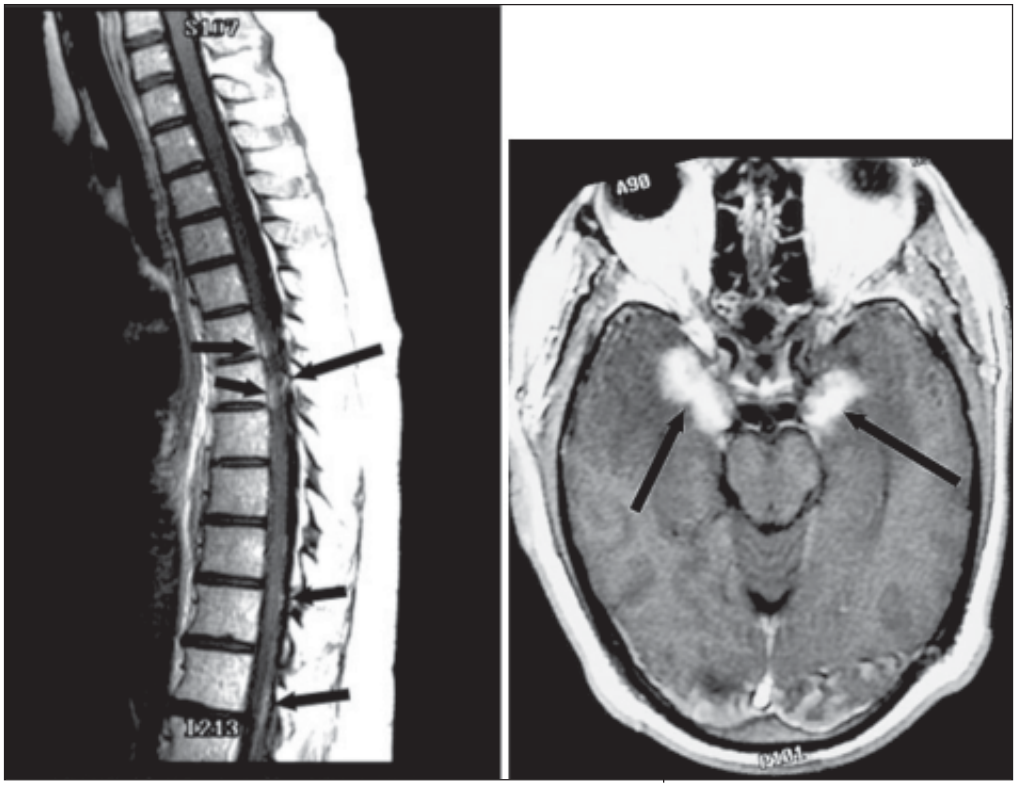

Figure 9. *Sagittal contrast enhanced T1-weighted MR image of the spine shows pial enhancement (arrows) consistent with leptomeningeal spread of leukemia and positive CSF cytology.*

DIRECT LEUKEMIC INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM

A. Meningeal disease

Meningeal leukemic infiltration

a. leptomeningeal spread (leukemic meningitis)
i. diffuse
ii. focal
b. dural leukemic infiltration
i. diffuse
ii. focal dural based leukemic mass (chloroma)

Mimics of leukemic meningeal disease

a. leptomeningeal/subarachnoid
i. infectious meningitis
ii. chemical arachnoiditis/meningitis-
(i.e. secondary to intrathecal chemotherapy)
b. dural
i. post-shunting/Ommaya reservoir meningeal fibrosis

B. Nonmeningeal disease

Brain parenchyma

a. chloroma
b. other leukemic mass

Head and neck

a. orbital disease
i. extraoccular infiltration
ii. other intraorbital involvement
b. skull base
c. paranasal sinus

Bone marrow abnormality

a. leukemic infiltration
b. decreased T1 SI secondary to chronic disease or conversion to hematopoietic marrow

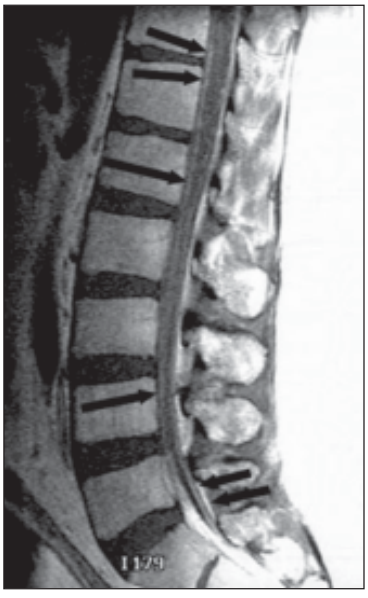

Figure 10. *MR with contrast demonstrated diffuse linear and slightly nodular subarachnoid enhancement (arrows). CSF cytology were negative for blasts. This is presumed to represent chemical arachnoiditis secondary to chemotherapy and multiple traumatic taps.*

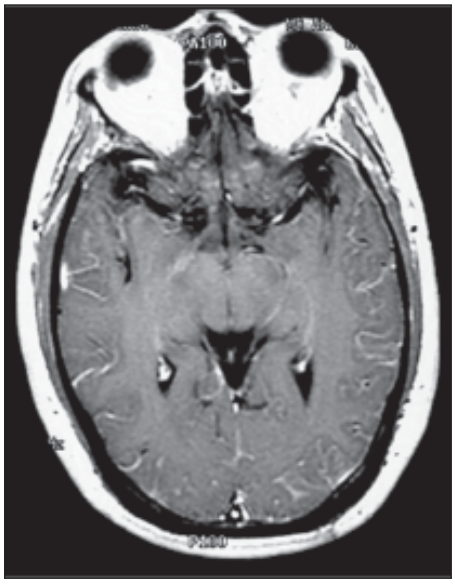

Figure 11. *MR with Gd (A) showed pial enhancement consistent with leukemic meningitis, confirmed by cytology. He was given intrathecal ARA-C and developed thrombocytopenia, with subsequent lumbar puncture showing red blood cells in the CSF. Despite platelet transfusion, he continued to ooze into his subarachnoid space, and ultimately had a massive subarachnoid bleed. The studies of Price and Johnson demonstrated that CNS leukemia is primarily a pial disease. The earliest evidence of leukemia is detected in the walls of pial vessels while the leukemic infiltrate can extend to the deep perivascular spaces. There is also a diffuse inflammation of the vessel wall and therefore the rupture of the vessels can occur.*

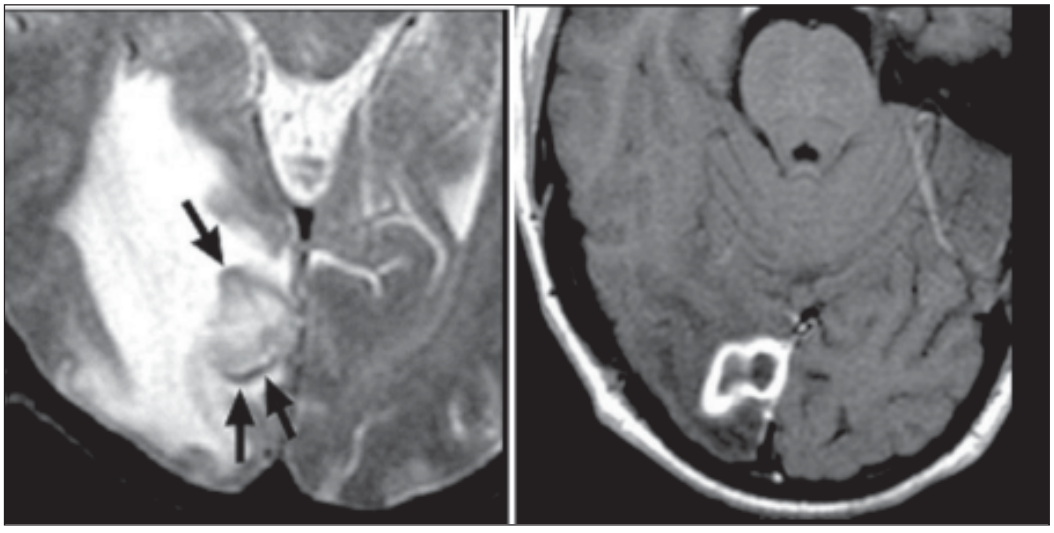

Figure 12. *MR showed a right occipital mass. On T2 (A), a ring of signal hypointensity (arrows) suggests abscess. Ring enhancement is seen with Gd (B). An Aspergillus abscess was discovered at surgery.*

OTHER CNS DISEASE RELATED TO UNDERLYING AND SECONDARY EFFECTS OF MALIGNANCY:

A. Hematologic/ Cerebrovascular

Intracranial hemmorhage

a. extraaxial

b. intraparenchymal

Sinovenous thrombosis

Cerebral infarction

B. Paraneoplastic Syndromes

Progressive necrotizing myelopathy

C. Infection

Sinusitis

a. bacterial

b. fungal

Intracranial infection

a. IC spread of opportunistic/fungal sinusitis

i. meningitis, extraaxial empyema

ii. brain abscess

b. hematogenous spread

i. meningitis

ii. brain abscess

iii. encephalitis

c. other (i.e. IC spread of other extracranial infection)

Other head and neck infection

DISEASES RELATED TO TREATMENT

A. Direct effect of chemotherapy or radiation therapy

Diffuse necrotizing leucoencephalopathy

Mineralizing microangiopathy

Other brain effects of chemotherapy

a. reversible MR changes with Cyclosporine A
b. enhancement/necrosis (?) at shunt entrance site
c. cerebellar degeneration secondary to Cytarabine

Spine involvement
a. chemotherapy induced (necrotizing) myelopathy

Second primary malignancy?

B. Effects of bone marrow transplantation (BMT)

Graft vs. Host disease (GVHD)
a. direct brain involvement (very rare)

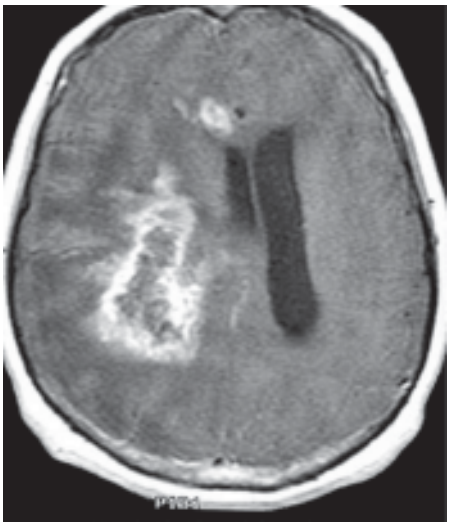

Figure 13. *MRI (postcontrast T1) demonstrated an enhancing mass in the right hemisphere. Biopsy revealed only necrosis (diffuse necrotizing leucoencephalopathy).*

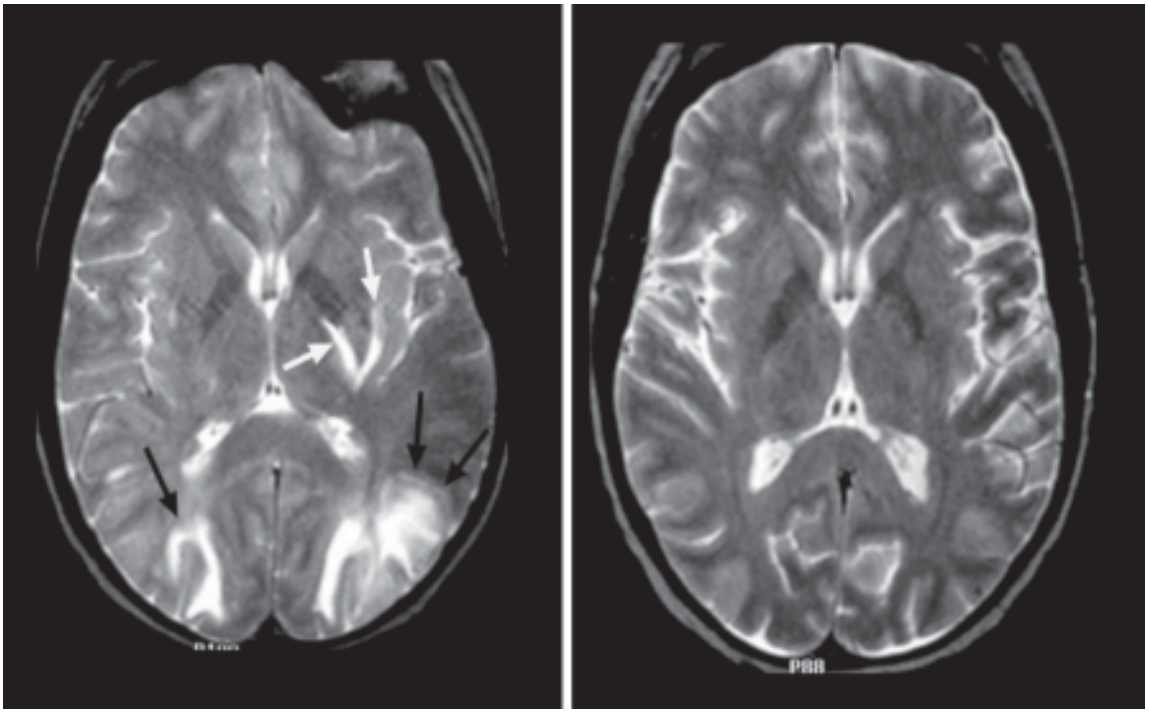

Figure 14. *This patient had recieved Cyclosporine A following bone marrow transplantation. MRI (A) demonstrates T2 hyperintensity in the occipital lobes (black arrows) and left internal/external capsules (white arrows). Following discontinuation of the Cyclosporine A, the symptoms and MR changes reversed (B) (reversible MR changes with Cyclosporine A).*

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