

Spontaneous chronic subdural hematoma development in chronic myeloid leukemia cases at remission phase under maintenance therapy, management strategy - a series with literature review

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Abstract: Chronic subdural hematoma (CSDH) is common sequel of trauma and rarely associated with anticoagulant therapy, antiplatelet, chemotherapeutic drugs, arteriovenous malformation, aneurysms and post-craniotomy. However its occurrence is very unusual with systemic haematological malignancy and mostly reported with acute myeloid leukemia; however incidence of SDH occurrence in chronic myelogenous leukemia (CML) is very rare. CML is a haematological malignancy characterized by chromosomal alteration, pathologically represents increased proliferation of the granulocytic cell line without loss of capacity to differentiate. CML has three phases – remission phase, accelerated phase and blast crisis. About 85 % of patients present in remission phase of disease and carries a favorable prognosis. As intracranial, subdural hematoma usually occur in the accelerated phase or blast crisis phase or extremely uncommon during chronic remission phase, although only those affected, who are neglecting therapeutic medication or discontinued therapy or rarely as an adverse effect of medications. However, important role of neurosurgeon lies in early detection and correction of platelet count and associated hematological abnormality as quite sizeable proportion of cases may not need surgical intervention instead can be managed conservatively under regular supervision in association with oncologist colleague, but few cases may need urgent surgical intervention. So, selecting a subgroup of CML cases in the remission phase requiring surgical intervention, presenting with CSDH is not only challenging, as failure to make an informed and timely precise decision can lead to catastrophic worse outcome and even mortality. So, purpose of current article is to formulate the management therapeutic plan. Authors report three cases of CML in chronic remission phase, receiving treatment under guidance of Haemto-oncologist at our institute presented with spontaneous chronic SDH. The mean age was 36 years (range 29- 44 years), 66% were male, headache was presenting feature in all 100% (n=3), 66% cases were hemiplegic and 33% unconscious each, in 66% cases CSDH were located on right fronto-temporal region and 33% had small left sided thin CSDH. About were

66% cases (n=2) were managed surgically by burr hole placement and drainage drain placement while 33% case (n=1), who had thin CSDH was managed conservatively. Favorable outcome was observed in 100% cases (n=3) Outcome was favorable in all of our cases.

Key words: chronic myeloid leukemia, remission phase, chronic subdural hematoma, management

Introduction

Chronic subdural hematoma (CSDH) is an important cause of morbidity and usually caused by previous trauma, post-craniotomy surgery, thrombocytopenia, chronic alcoholism, radiation induced or intake of various medications including anticoagulants, antiplatelets or following rupture of intracranial aneurysms (1-4, 5), arterio-venous malformations (5) and cocaine drug abuser (8). It is very rarely reported to occur with intracranial neoplasms like meningioma (10), rhabdomyosarcoma (15). Association of C SDH is reported with lymphoma (16), choriocarcinoma (18), however, its occurrence is very unusual with systemic haematological malignancy and mostly occurred in association with acute myeloid leukemia. CSDH occurrence is extremely uncommon in chronic myeloid leukemia (CML), but few cases are reported in form of isolated case –report, tend to occur only in the accelerated phase of CML. Authors present three cases of chronic SDH occurrence in chronic remission phase of CML, who were treated at hemato-ontological clinic, were in the remission phase of CML, developed CSDH, managed successfully.

Case illustration one

A 35 year male reported with complains of with insidious onset gradually progressive

headache, vomiting, left sided hemiparesis and altered sensorium for last two weeks with no antecedent history of trauma, alcohol or oral anticoagulants or antiplatelets intake. He was diagnosed as case of CML, about 18 weeks back. At present, he was in the chronic remission phase receiving maintenance dose of oral tyrosine kinase inhibitor imatinib mesylate. On neurological examination at admission, he was drowsy with Glasgow Coma Score (GCS) of 13 with pupils' bilaterally normal size and briskly reacting to light. Left sided seventh nerve upper motor neuron paresis and spastic hemiparesis along with brisk deep tendon jerks and plantar were bilaterally extensor. Haematological investigations were within normal limit with mild leucocytosis.

CT scan head, revealed presence of right sided fronto-parietal hypodense chronic SDH, volume were about 60 ml and causing mass effect with 8 mm midline shift to the left (Figure 1). A right frontal and parietal burr hole were made and hematoma evacuation was carried out under local anesthesia and intravenous sedation. Post-operative NCCT head subsidence of mass effect with no residual CSDH. He gradually improved clinically and was discharged in stable condition with GCS of 15.

He was re-admitted with similar complaints of headache and right sided

weakness 6 months later. Hemogram and coagulation profile were within normal limits. Repeat NCCT head, showed mixed density fronto-parietal SDH on contra lateral left side (Figure 2). Magnetic Resonance Imaging (MRI) was carried out to rule out brain parenchyma lesion which revealed presence of sub-acute subdural hematoma over left frontoparietal region (Figure 3). He underwent left sided frontal and parietal burr hole and hematoma evacuation with uneventful recovery. Histopathology report and cytopathological analysis of subdural fluid were inconclusive for any malignant infiltration of dura mater or subdural membrane or subdural fluid. He was doing well without any further recurrence; however, maintenance medication for CML was continued in consultation with haematology department. Patient was still in chronic phase at twelve months following first surgery.

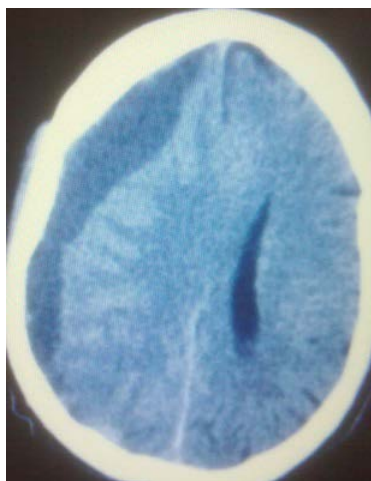


Figure 1 - Pre-operative non-contrast CT scan head showing right sided hypodense chronic SDH, extending over fronto-parietal region causing mass effect (Case 1)

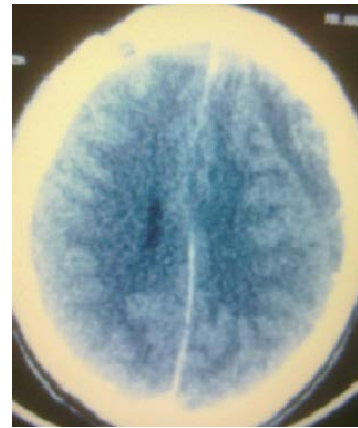


Figure 2 - Repeat non-contrast CT scan head at six months following first surgical burr hole drainage showing fresh SDH development on contralateral side located overleft fronto-parietal area (Case 1)



Figure 3 - MRI brain, T2WI,axial section at six months follow-up to correlate CT findings, following first surgical evacuation of SDH showing no residual SDH ,but newly developed SDH on contralateral side located overleft fronto-parietal region (Case 1).

Case illustration two

A 44 year male was referred to neurosurgical emergency services from

haematology department with outpatient department with complains of persistent headache and progressive left hemiparesis for one month. No other relevant history or co morbid illness was elicited. He was diagnosed with CML about one year back and presently in chronic remission phase on maintenance therapy. On neurological evaluation, his GCS was 15/15, with left sided upper motor neuron type facial nerve paresis. Power in left upper and lower limb was 4/5. Haematological parameters were within normal limits.

CT scan head revealed presence of chronic SDH in right fronto-temporo-parietal region measuring approximately 45 ml with mass effect and midline shift of 5 mm. He underwent elective burr hole drainage of SDH. Intra-operative, altered blood with thickened pseudo-membrane surrounding it. Histopathological evaluation of dural membrane biopsy and cytopathology of subdural fluid was also non-contributory. Post-operative NCCT head showed near-complete evacuation of SDH and relief of mass effect. He had uneventful postoperative phase with recovery of hemiparesis. He tolerated surgical procedure well. At the last follow-up 6 months following surgery, he was doing well and continuing to receive maintenance therapy of tyrosine kinase inhibitor.

Case illustration three

A 29 year old female reported our outpatient services with gradually worsening headache for 3 weeks. She also had no other significant history except diagnosis of with CML, six months back and currently on in chronic phase on maintenance therapy under

supervision of haematologist. Neurological examination was unremarkable and haematological investigations showed platelet count and coagulation profile within normal limit.

NCCT head revealed hypodense left side thin fronto-temporal chronic SDH measuring about 15 ml. (Figure 4) the findings were confirmed on MRI (Figure 4). She responded well to conservative management without further increase in size. She was kept on regular follow-up on outpatient services basis for six months till her follow up CT scan revealed complete resolution of hematoma.

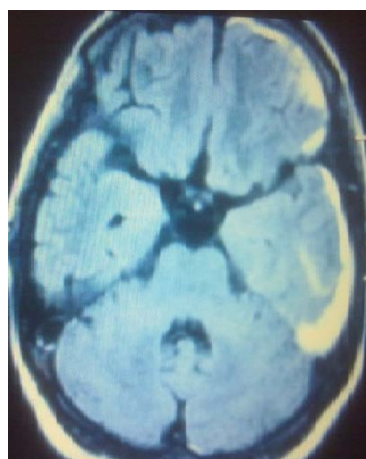


Figure 4 - Non-contrast enhanced MRI brain T1WI, axial section hyperintense signal intensity, SDH showing over left side fronto-temporal area (Case- 3)

Discussion

Chronic Myelogenous Leukemia (CML) is a haematological malignancy characterized by chromosomal alteration, typically showing reciprocal translocation between chromosomes 9 and 22, observed approximately in 90% cases. Pathologically

represents increased proliferation of the granulocytic cell line without loss of capacity to differentiate.

The clinical course of CML can be sub-classified into three phases – chronic phase, accelerated phase and blast crisis. About 85 % of patients of chronic remission phase carry a favorable prognosis, if kept on long- term tyrosine kinase inhibitors maintenance therapy. However, chronic stage can also progress to either accelerated phase or blast crisis phase accompanying with unfavorable prognosis, if left untreated in chemotherapeutic resistant cases. Predominant factor for differentiating among both phases is presence of 10-19 % myeloblasts and greater than 20 % myeloblasts in peripheral blood smear or bone marrow examination in former and latter respectively (7, 20).

However, with advent of newer selective tyrosine kinase inhibitors, treatment of CML is revolutionized with improved outcome, 80-90 % long- term survival rates. (12) During course of therapy very few cases may develop major intracranial bleeding, who were receiving medication for CML treatment under combined supervision of haematologist and oncologist.

Chronic subdural haematoma contains an inner and an outer capsule. The capillary endothelial cells lining of capsules contains cytoplasmic protrusions and fenestrations. Mean age in the present series was 36 years (range 29-44 years) compared to 50 years as mean age at presentation, with male to female ratio was 2:1 compared to 1.3: 1 as reported in Jonte et al series. (6) Patients in chronic phase

of disease had favorable outcome with 100% survival rate during short term follow up. Authors advocated further evaluated of these cases should be carried to rule out systemic haematological malignancy. (6)

Spontaneous SDH occurrence in association with solid malignancy may have additional history of precipitating factors like head injury, however such history is usually absent in haematological malignancy specifically acute myeloid leukemia (14); although rare, an only very few cases have been reported in association with other systemic haematological malignancy (1, 2, 3, 9, 11, 17, 19).

Exact mechanism of SDH occurrence in is still debated, various postulates are put forward including – malignant cell deposits causing occlusion of dural blood vessels, rupture of occluded dural blood vessels into subdural space and tumor necrosis in metastatic deposits, thrombocytopenia secondary to chemotherapeutic agent therapy, development of disseminated intravascular coagulation disorder. Even direct secondary dural leukemic deposits are postulated to explain repeated recurring SDH following surgical intervention. Our first case had right sided frontotemporal CSDH and after six months following evacuation, developed CSDH on contralateral side necessitating surgical intervention on that side also. Cases with diagnosed case of CML, who are put chemotherapeutic treatment, may carry increased risk of intracranial haemorrhage depending on stage of primary disease. In a study conducted by Druker et al, observed incidence of intracranial haemorrhage in CML

patients, who are on medical treatment in the range of – 5 % in blast crisis phases, 1 % in accelerated phase and almost negligible risk of 0.6 % in the chronic remission phase. (4). the occurrence of chronic SDH in chronic phase of disease is extremely uncommon. However, our cases were very unique as all were in chronic remission phase, who were on regular treatment under care of haematologist supervision receiving tyrosine kinase inhibitor imatinib mesylate or Dasatinib, according to optimal requirement in response to therapy. However, histopathological evaluation of biopsy specimen of dural membrane ruled out presence of any malignant cell deposit and further cytopathology of subdural fluid was negative for malignant cells in all our cases.

However, mechanism of intracranial bleed remains elusive despite presence of normal haematological parameters i.e., platelet count and coagulation profile, dysfunction of platelet aggregation and reduced α 2-plasmin inhibitor factors and even acquired Van Will brand disease was also incriminated. (9, 13) Giuffrè suggested role hormonal factors, in addition to mechanical, hematogenic and vasogenic factors, could play an important role in the pathogenesis of these hematomas. (21)

CSDH can either increase in volume size and clinically presents with focal neurological deficit and mass effect or extremely rarely can even show slowly resolution over time. Mechanism of gradual progression in size of the chronic subdural hematomas were attributable to CSF passage caused due to osmolarity gradient, which in turn caused by blood degradation products. However,

recently proposed mechanism attribute to leaking capillaries causing repeated microhaemorrhages taking place into the haematoma cavity. The leaking component may exceed the resorptive capacity of chronic subdural hematomas, leading to its enlargement all of our patients were clinically and haematologically in remission phase with strict supervision and guidance of therapy under haematologist at our institute. All the patients had platelet counts and coagulation profile within normal range. (21) These may be cause of deterioration of our two cases,

Treatment of subdural hematoma is usually surgical evacuation in symptomatic cases, however, CSDH occurring secondary to coagulation disorder or hematological malignancy may even responds to correction of haematological abnormality and with relief of mass effect or resolution of ASDH even without any need of surgical intervention. As our two cases needed surgery and 33 % cases responded to conservative treatment. Surgical approach of CSDH management include burr hole craniostomy with or without drain placement, mini craniotomy or rarely craniotomy and excision of thick membrane in those cases with extremely thick membrane or repeated failure of burr hole craniostomy. In the current study, two out of three cases, required surgical evacuation of SDH and underwent burr hole evacuation by placing frontal and parietal burr holes and irrigation and drain was also kept for three days following surgical procedure. In the postoperative period scan revealed complete evacuation. Fortunately third case did not required surgical intervention. Our cases had

no complication except one case (case1), who during follow-up period, developed new onset CSDH on contralateral side at six month following initial surgery, which also required surgical evacuation and all three cases are under regular follow-up on maintenance therapy under hematologist. Prognosis of CML associated with CSDH in remission phase is definitely better than the blast or crisis phase. In 2015 authors reported development of CSDH ma during

accelerated phase of Chronic Myeloid Leukemia presented with seizure, who had and rapid progression course and had fatal outcome despite surgical intervention, however, CSDH was diagnosed after a delay, accordingly author further recommends timely selection of potential surgical candidate as requirement of ASDH is critical in addition to timely surgery to provide for good neurological outcome along with high degree of suspicion is must. (23)

TABLE I
Summary of chronic myeloid leukemia cases, who developed chronic subdural hematoma and management outcome

Sl. No	Age (Year) /Sex	Clinical features	NCCT Head	CML stage/ Chemo-therapy	Interval of SDH occurrence followings diagnosis of CML	Hematological investigation	Management	Follow-up	Remark
1	35/M	Headache, unconsciousness	Right fronto-temporal	Chronic remission / yes	4 months	Within limit	Right sided burr hole, after 6 months burr hole on left side	2 years doing well	Fresh Chronic SDH on contralateral side 6 month following the first surgery
2	44 /M	Headache, Hemiparesis	Right fronto-parietal	Chronic remission / yes	One year	Within limit	Burr hole drainage	18 months well	-
3	29/ F	Headache	Left thin frontotemporal region	Chronic remission / yes	Six months	Within limit	Conservative	17 months doing well	-

Conclusion

Chronic subdural hematoma can be associated with recent history of physical trauma, drug intake, coagulation disorder and very rarely haematological malignancy. Chronic myeloid leukemia can be predisposing factors especially during blast crisis phase. All our cases were already diagnosed case on maintainance therapy for CML in the chronic remission phase presented with headache and focal neurological deficit. Two out of three were managed surgically and rest one responded favorably to medical therapy. It is especially important to select subgroup of patients among all cases, who are potential surgical candidate, otherwise delay in selection and treatment can produce catastrophic event. It is prudent to be vigilant in all case of chronic CML and other hematological malignancy, especially those cases developing headache or focal neurological deficit and haematologist should also be warned about possibility and minimum CT scan head must be carried out at the first suspicion of any developing intracranial pathology mass lesion without wasting golden time.

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