



Intracranial Hemorrhage Focused on Cancer and Hemato-oncologic Patients

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Abstract

Intracranial hemorrhage (ICH) is the most fatal type of stroke and has the highest rate of disability. It is seen in less than 10% of cancer patients, including known intracranial neoplasms. Intratumoral hemorrhage and coagulopathy are the most common etiologies. ICH most commonly occurs supratentorially, in the cerebral parenchyma. The most common

cancers associated with ICH are intracranial metastases, followed by glioblastoma multiforme and hematologic malignancies. Among hemorrhagic metastases, melanoma, lung, and breast cancers are the most common primary tumors. The exact mechanism of intratumoral hemorrhage is unknown, although vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMP) appear to play an important role. Most cancer patients with ICH are symptomatic. Change in mental status, hemiparesis, and headaches are the most common clinical presentations. A non-contrast head computed tomography (CT) scan is the

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initial diagnostic step if ICH is suspected. There are no specific guidelines for ICH management in cancer patients. Blood pressure needs to be controlled, and coagulopathy has to be corrected. Surgical interventions might be life-saving, especially in large hemorrhages in the posterior fossa. Overall, cancer patients have worse clinical outcomes than the general population when they develop ICH. Patients with coagulopathy have the poorest prognosis.

Keywords

Intracranial hemorrhage · Cancer · Brain tumor · Glioblastoma multiforme · Brain metastases · Intratumoral hemorrhage · Coagulopathy · Thrombocytopenia

Introduction

Intracranial hemorrhage (ICH) is the most fatal type of stroke and has the highest rate of disability among the survivors [64]. It can be defined as any bleeding that occur inside the cranial vault. This includes bleeding inside the brain tissue itself which is called intraparenchymal hemorrhage (IPH) and inside the brain ventricles known as intraventricular hemorrhage (IVH) and bleeding that occurs between the brain and its surrounding covers including subarachnoid hemorrhage (SAH), subdural hematoma (SDH), and epidural hematoma (EDH). Although the incidence of ICH in cancer patients is low [58], a good understanding of the relation between ICH and cancer is essential, as the pathophysiology, management, and clinical outcomes can be different from what is encountered in the community.

Etiology

Patients with cancer tend to have ICH from different pathologies comparing to the general population. Intratumoral hemorrhage and coagulopathy are the most common etiologies for ICH in cancer patients. Navi et al. retrospectively analyzed data of 208 cancer patients with IPH or SAH who presented to a single cancer

center over a period of 7 years [48]. Sixty-one percent of cases were caused by intratumoral hemorrhage and 46% by coagulopathy. Thirty-three percent had multifactorial causes and 21% had both intratumoral hemorrhage and coagulopathy. Not surprisingly, solid tumors were more associated with intratumoral hemorrhage, whereas coagulopathy was more often found to be the cause of ICH in hematological malignancies. Interestingly, hypertension, which is the most common cause of spontaneous ICH in the community, only caused around 5% of ICH in cancer patients, which highlights the unique mechanisms of ICH in the setting of neoplasms [48, 53, 60, 69].

Other, but less frequent, etiologies were trauma (6%), hemorrhagic conversion of ischemic strokes (4%), cerebral venous thrombosis (2%) (which can be resulted either from hypercoagulability or neoplastic venous sinus compression) [48, 66], and aneurysmal rupture (2%).

Rare causes that are unique to patients with cancer include leukostasis which can occur in patients with leukemia when peripheral white blood cell counts rise above 100,000 cells/mm³ and hyperviscosity [48, 66].

Besides intraparenchymal location, ICH in patients with cancer can involve other intracranial compartments [24, 34, 48, 68, 72]. SAH usually occurs in the setting of coagulopathy, trauma, or intratumoral hemorrhage that is adjacent to the cortex. Aneurysms and arteriovenous malformations are much less common etiologies of SAH in cancer patients comparing to the general population [48]. It is worth mentioning that when aneurysmal SAH occurs in patients with cancer, other atypical types of aneurysms, like mycotic and neoplastic (although the latter is extraordinarily rare), should be kept on the differential. Neoplastic and mycotic aneurysms are fusiform, typically develop in distal middle cerebral artery branches, and are most commonly associated with atrial myxoma, choriocarcinoma, and lung carcinoma [56, 66].

SDH is found frequently in patients with cancer and usually results from coagulopathy or from trauma [55]. A recent craniotomy can

lead to SDH. Less frequently, the cause of SDH can be intratumoral hemorrhage from dura mater metastases [33, 46, 50]. In one report, 15–40% of patients with dural metastases have a coexistent SDH, mostly chronic [33].

Like SDH, EDH usually results from trauma or coagulopathy. In rare cases, it may occur from calvarial or dural neoplasms (primary or metastatic) [43, 66].

Epidemiology

Intracranial hemorrhage is responsible for about 50% of cerebrovascular events in patients with cancer and is more likely to be symptomatic than ischemic strokes [24]. Murphy et al. identified all patients diagnosed with spontaneous ICH from 2002 to 2011 in the Nationwide Inpatient Sample. Among 597,046 identified ICH patients, 22,394 (3.8%) had systemic cancer [47]. In patients who present as spontaneous ICH, brain neoplasm was found to be the underlying etiology in about 1–8% of cases [2, 32, 58, 59]. A prospective study of 692 patients who presented with ICH found intracranial tumor related to the ICH in 7.2% of the cases [58]. In another large autopsy series of ICH, an underlying and unsuspected cancer was discovered in only 4 of 430 (1%) cases [32, 58]. Similarly, a recent meta-analysis showed that an intracranial malignancy (including glioblastoma) as a cause of spontaneous ICH in young adults was rare, accounting for 2.3% of cases [28]. On the other hand, the incidence of ICH in known intracranial neoplasm patients was 2.4% according to a large prospective study that included 2041 patients with intracranial neoplasms [58].

ICH in cancer patients occur almost equally in both genders [68]. The median time from cancer diagnosis to ICH occurrence differs between patients based on the cancer type. In one study, the median time was 28 months for solid tumors, 22 months for hematologic tumors, and 6 months for primary brain tumors [48].

As far as ICH location goes, about three quarters of ICH in cancer patients are supratentorial. Infratentorial ICH sites are more common in the cerebellum than the brain stem.

Among intracranial compartments, bleeding occurs most frequently inside the brain parenchyma, followed by the subdural and then the subarachnoid spaces. Epidural location is less frequently encountered. In almost 25% of times, multiple hemorrhages can occur simultaneously, and in about 20% of cases, there are intraventricular hemorrhages [48, 58, 68].

Overall, any type of intracranial tumor can cause ICH, although the frequency varies widely among different neoplasms [58]. Usually, fast-growing and highly vascularized tumors with an irregular and fragile vascular architecture are most frequently associated with ICH [37]. Several tumors, particularly malignant ones, have an increased predilection for intratumoral hemorrhage [24, 31, 48, 58, 72]. The leading causes of tumor-related ICH were metastases of extracranial origin (36%), followed by glioblastoma multiforme (GBM) (30%) [38, 58]. In one retrospective study of ICH in patients with cancer, Navi et al. found that the cancer contributing to hemorrhage was a solid tumor in 68% of cases, a primary brain tumor in 16% of cases, and a hematologic tumor in 16% of cases.

Melanoma (15%), lung (14%), breast (7%), and renal cell (4%) cancers are the most common systemic solid tumors associated with ICH [48]. Their frequent association with ICH is partly explained by their ubiquity – these tumors have a high incidence in the population and account for most brain metastases – and their histological composition, which has elements of neoangiogenesis, tumor cell necrosis, and parenchymal blood vessel invasion [5, 35, 57]. On the other hand, thyroid cancer, hepatocellular carcinoma, and choriocarcinoma are rare causes of brain metastases but have an unusually high predisposition to hemorrhage, accounting for their overrepresentation of ICH in cancer series [11, 24, 35]. In addition, although prostate cancer rarely metastasizes to the brain, it accounted for a sizeable proportion (5%) of ICH in a recent clinical series of patients with cancer. This increased incidence compared to prior reports may be due to improvements in prostate cancer therapy, which may have altered the natural history of disease allowing for longer survival and increased risk of cerebrovascular complications [48].

Of primary brain tumors, glioblastoma multiforme (GBM) is most frequently associated with ICH, because it is the most common primary brain neoplasm and because its tumor cells are highly invasive and destructive [31, 34, 58, 72]. With their fragile retiform capillaries, oligodendrogliomas are also predisposed to hemorrhage even when low grade, despite the fact that they are much less frequent tumors than GBM [37]. Furthermore, benign neoplasms, including meningiomas, can also cause intratumoral hemorrhage. Benign neoplasms accounted for 23 of 110 (21%) and 9 of 50 (18%) cases of intratumoral hemorrhage [34, 58]; however, bleeding from meningioma is relatively rare. Wakai et al. found meningioma to cause only 4 of the 310 cases of intracranial neoplasm who presented with ICH [68]. Highly vascular meningotheliomatous and angioblastic meningiomas are most frequently the case. The majority of reported cases of meningioma associated with intracranial hemorrhage deal with SAH rather than IPH or hemorrhage within the substance of the tumor itself [36], probably due to their extra-axial location.

Hematological malignancies, particularly leukemia, are also frequently encountered in the setting of ICH in cancer patients. These tumors generally cause ICH through coagulopathy from severe thrombocytopenia or coagulation cascade dysfunction [24, 42, 48]. For instance, one study reported a mean platelet count of $13,500/\text{mm}^3$ in patients with leukemia (without intracranial invasion) and ICH. Despite the fact that lymphomas and leukemias can rarely metastasize to the brain parenchyma or arachnoid mater and cause brain hemorrhage, ICH still occur only in the setting of severe coagulopathy [24].

Pathophysiology

The mechanisms of ICH in cancer patients vary based on the cancer type. Solid tumors typically cause ICH from intratumoral hemorrhage. On the other hand, the vast majority of ICH in hematologic malignancies are related to coagulopathy and less frequently to leukostasis [24, 71]. In general, malignant and hypervascular neoplasms have the highest predilection for hemorrhage [31, 36, 48].

In 1889, Stephen Paget proposed the hypothesis of “seed and soil” which still, at least partially, explains the mechanism of metastases of systemic cancers to the central nervous system (CNS) [20]. In this hypothesis, tumor cells get their access to CNS capillary beds via hematogenous spread. Because 80% of the cerebral blood flow go to the anterior circulation, the majority of brain metastases and their related intratumoral hemorrhages are supratentorial as noted earlier. In addition, the “seed and soil” hypothesis can explain the propensity of certain tumors (e.g., melanoma) to establish brain metastases.

Although the exact mechanism that leads to intratumoral hemorrhage is still poorly understood, multiple factors that are possibly related to the pathophysiology have been identified. Several preclinical studies have suggested that new blood vessels induced by vascular endothelial growth factor (VEGF) have a propensity to lead to hemorrhage because of their fragility and permeability [10]. Immunohistochemical staining for VEGF was associated with intratumoral hemorrhage in surgical series [27]. Melanoma and renal cell carcinoma, two of the solid malignancies that their intracranial metastases have very high tendency to cause ICH, are highly vascularized tumors. Both of them are associated with angiogenesis and increased production of VEGF [40, 51].

In addition to VEGF, matrix metalloproteinases (MMP), which are substances that degrade extracellular matrix proteins and thereby allow for tumor invasion and metastasis [15], may also play a role in the pathogenesis of ICH secondary to malignancy. Jung et al. reported a study of 16 patients with brain metastases, 7 of whom had hemorrhagic complications and 9 did not. Patients in the hemorrhagic group had higher immunohistochemical expression of VEGF. In addition, they had evidence of increased basement membrane breakdown in the presence of immunohistochemical overexpression of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) [29]. This suggests the possible contribution of increased MMP protein elaboration to the pathophysiology of ICH in the setting of underlying brain tumors.

Besides overexpression of VEGF and MMP in tumor cells, imbalances in the fibrinolytic cascade, rupture of thin-walled fistulous or friable large vessels, rapid tumor growth, aberrant neovascularization, tumor necrosis, and vascular invasion [35–37, 56, 66, 68] are all factors that might participate in the pathophysiology of intratumoral hemorrhage. ICH might arise from the rapidly growing peripheral portion of the tumor or from adjacent damaged brain tissue too [36, 39]. The inherent capacity of choriocarcinoma for vascular invasion appears to be a particularly important factor in the pathogenesis of ICH in this highly hemorrhagic neoplasm [36, 61, 65].

As mentioned above, coagulopathy play the key role in the pathogenesis of ICH in hematological cancers. Coagulopathy typically result from abnormalities of platelets, coagulation factors, or both. It can also be iatrogenic as many cancer patients have indications for anticoagulation agents (e.g., warfarin and direct oral anticoagulants). Thrombocytopenia often occurs from bone marrow suppression secondary to chemotherapy or radiation, tumor infiltration, or intrinsic failure (in hematological malignancies) [66]. Impairments of the coagulation cascade generally result from liver failure, vitamin K deficiency due to poor nutrition, or disseminated intravascular coagulation (DIC) [24, 66].

In hematological malignancies, hyperleukocytosis, defined as peripheral blast count for more than $100,000/\text{mm}^3$, stands as a unique but less frequent mechanism of ICH, especially in acute leukemias. One suggested mechanism is plugging of small cerebral vessels by blast cells, resulting in local hypoxia and vessel destruction. Another possibility is invasion of blood vessels by nodular growth of leukemia cells [55].

Clinical Features

Ninety-four percent of patients with cancer who develop ICH are symptomatic when the hemorrhage is diagnosed radiographically [48]. This is not the case when ICH is identified at surgery or autopsy [24, 68]. In a series of

non-radiographically diagnosed ICH in brain tumor patients, Wakai et al. found about 42% of the patients with hemorrhage from brain tumors (other than pituitary adenoma) to be asymptomatic [68].

Clinical signs and symptoms of ICH in patients with cancer do not significantly differ from what is encountered in similar cases in the general population. Deterioration in the level of consciousness, hemiparesis, and headaches are the most common neurological findings following ICH [24, 36, 48, 58]. Nausea, vomiting, seizures, aphasia, hemisensory, and visual field disturbances are frequently seen [48], whereas unilateral dilated pupil and abducens cranial nerve (CN VI) palsy are present less often [58]. Coma can occur in 6–28% of cases [48, 58].

Diagnosis

As in all medical fields, clinical history and physical exam are the cornerstone in evaluating patients with cancer who might have ICH. History of trauma and coagulopathy (including taking anticoagulation medications) has a special importance. Acute onset of headaches, confusion, or focal neurological deficits such as aphasia, hemiparesis, hemisensory changes, and visual field disturbances are the main findings to look for. Asking about seizure-like activities is important as well.

When an intracranial central nervous system (CNS) process is suspected, a non-contrast head computed tomography (CT) scan is the first radiographic study to obtain because it can be done quickly, it is widely available, and it is pretty much sensitive for acute blood products detection [66]. As in other body parts, intracranial acute blood appears hyperdense on CT scan. If ICH is found, obtaining another CT study but this time with intravenous (IV) contrast along with CT angiography will add much more diagnostic value. Contraindications such as allergy to iodinated contrast and renal insufficiency need to be considered before proceeding with those studies. CT angiography of the head is particularly helpful in revealing underlying vascular malformations, an important etiology for ICH. Furthermore,

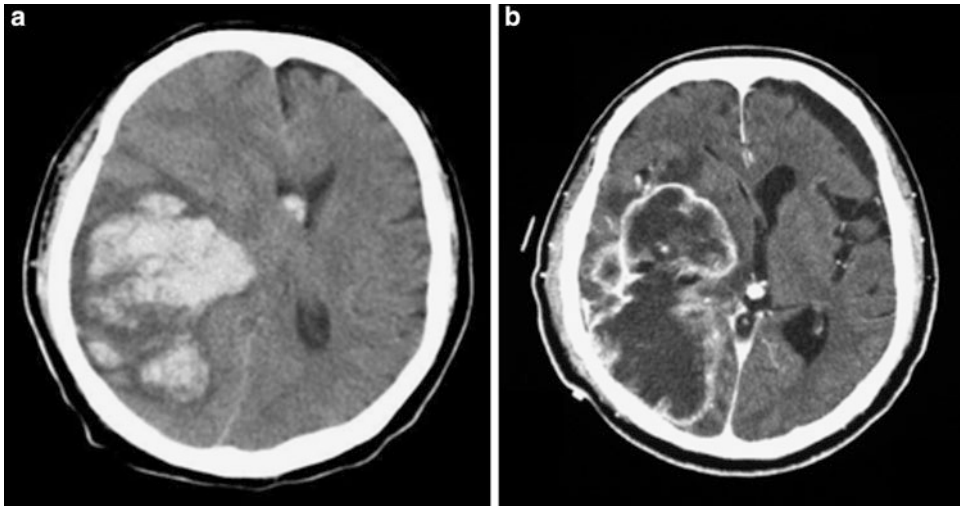


Fig. 1 (a) Axial CT head without contrast at admission of a 66-year-old male revealing a huge lobar acute hemorrhage in right temporoparietal region. (b) A follow-up CT head with contrast performed 2 months after the initial scan demonstrating giant mass with ringlike enhancement in the

same region as the previous hemorrhage. (Photo is used with permission [Taniura S, Okamoto H, Tanabe M, Kurosaki M, Mizushima M, Watanabe T, Huge lobar intracerebral hemorrhage by glioblastoma multiforme. *J Neurooncol* (2007) 82:117–118. Fig. 1: page 118])

a “spot sign,” which indicates active extravasation of blood products and fairly predicts hematoma expansion, might be found [67].

Cancer-related ICH shows distinct radiographic features, which should be carefully considered when interpreting ICH on CT scan [58] (Fig. 1). An atypical location of the hemorrhage can point at the possibility of the presence of a tumor. A bleeding in the cortical-subcortical junction or close to the dural membranes such as the falx or the tentorium or located close to major cerebral veins or sinuses can be related to tumor, comparing to deep basal ganglia and lobar locations which are more typical for hypertensive and cerebral amyloid angiopathy-related hemorrhages, respectively. Heterogeneous and irregular or ring-shaped appearance of the bleeding, the presence of calcification, and multifocal location are all clues that can suggest an underlying neoplasm. More importantly, contrast enhancement can reveal a tumor that would otherwise be concealed by the blood clot. Usually, peritumoral vascularization enhances, particularly, at its margins. Furthermore, excessive edema surrounding the hematoma on CT scan is often a very important clue to an

underlying neoplasm because it is only rarely seen in the acute phase of spontaneous ICH [58]. One study reported a positive predictive value of 71% for underlying neoplasm if the vasogenic edema to mean hematoma diameter ratio was greater than 100% [63]. Additionally, persistent edema and delayed hematoma evolution are also suspicious for intratumoral hemorrhage [4].

Brain magnetic resonance imaging (MRI) with contrast offers better resolution than CT and shows all the findings that suggest tumor-related ICH noted earlier (Fig. 2). However, it takes much more time to be performed, in addition of being more costly. A special importance that favors MRI over CT scan is its ability to better evaluate for alternative etiologies of ICH. Ischemic stroke with hemorrhagic conversion (via diffusion-weighted imaging), venous sinus thrombosis (thrombosed veins demonstrate flow voids on pre-contrast images and restricted enhancement on post-contrast images), and amyloid angiopathy (lobar microhemorrhages on susceptibility-weighted sequences) are some examples [66].

Digital subtraction angiography (DSA) is an invasive diagnostic procedure that is still

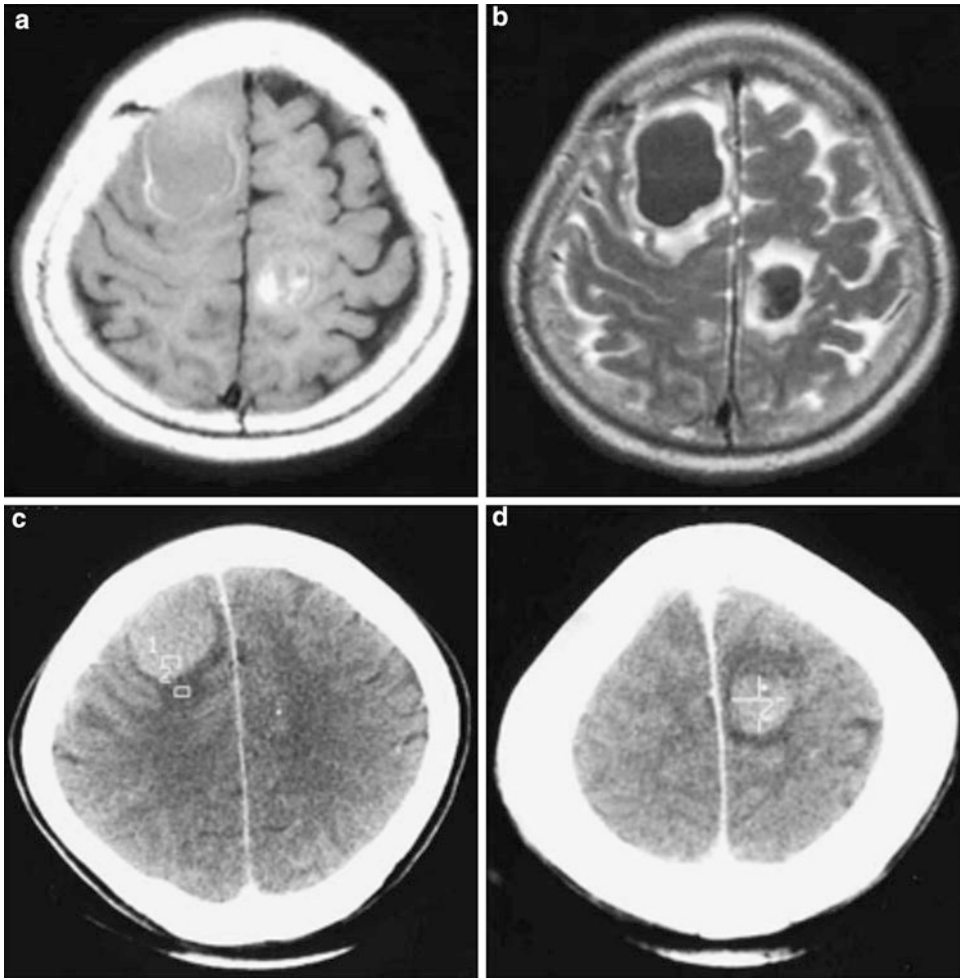


Fig. 2 This is a 69-year-old female with history of metastatic non-small cell lung cancer. She has left and right frontal hemorrhagic metastases. (a) MRI T1 and (b) MRI T2, both axial cuts, show acute to early subacute hemorrhages which appear isointense to hyperintense (bright) on T1 and hypointense (dark) on T2. Vasogenic edema

surrounding the hemorrhages is easily identifiable on T2 (hyperintense). (c) and (d) CT head without contrast, axial cuts, show the same hemorrhagic metastases which appear as hyperdensities (bright). Vasogenic edema appears as hypodensity (dark) on CT. (Photo is used with permission from Ref. [29], p. 258)

sometimes used in the setting of ICH evaluation, mainly to rule out vascular malformations. In patients with cancer, abnormal tumor vessels and early venous filling were demonstrated in some cases, along with tumor mass effect [36].

Practically, a short-term neuroradiological follow-up is advisable in all cases in whom the clinico-radiological features do not correspond to the usual pattern of intracerebral hypertensive hemorrhage [47], although the timing and indication for contrast-enhanced brain MRI in

the diagnostic evaluation of idiopathic IPH is more controversial [66]. In a study that included 148 patients with unexplained IPH evaluated with brain MRI, only 1 patient was found to have an underlying tumor [30]. In addition, acute IPH may obscure a tumor, leading to a false-negative study if MRI is performed too early [23]. With that being said, unless there is a high suspicion for cancer or another cause of IPH frequently detected on MRI (such as hemorrhagic conversion of an ischemic stroke or amyloid angiopathy), probably

it is better idea to perform MRI 4–12 weeks after the ictus in order to enhance its diagnostic yield [66].

Besides diagnostic imagings, a focused laboratory evaluation should be performed as soon as possible in fairly all cases of ICH. Complete blood count (CBC), coagulation profile (e.g., PT, aPTT, and INR), and disseminated intravascular coagulation (DIC) panel (e.g., D-dimer and fibrinogen levels) are essential. A platelet function test can be checked if the patient is going to have an emergent surgical intervention. Moreover, if DIC is suspected, a peripheral blood smear should be obtained to evaluate for schistocytes [66].

Management

Since there are no specific protocols for management of ICH in cancer patients, existing guidelines for IPH, SDH, and SAH should be applied in those cases [13, 26, 66]. As in any serious and life-threatening medical illness, the management of cancer patients who present with ICH starts with a quick and focused evaluation of airways, breathing, and circulation (ABC). When the diagnosis of ICH is established, an urgent and, in case of rapidly declining mental status or ongoing clinical seizures, an emergent, neurological and neurosurgical consultation is mandatory. Admission to a dedicated intensive care unit with neurologic specialization is advised because that may decrease mortality in ICH patients according to a retrospective review of outcome data from the Project IMPACT database of intensive care units [18].

Pharmacologic

In patients with IPH, blood pressure should be controlled immediately after ictus similar to cases of spontaneous ICH. Intravenous antihypertensive agents, including nicardipine infusion, are usually used to rapidly control blood pressure. In a large prospective study of patients with spontaneous ICH, a systolic blood pressure (SBP) reduction to less than 140 within 1 h after randomization comparing to standard

management (keeping SBP < 180) was safe. Although there was a statistically significant improvement in functional outcomes, the rates of severe disability and death were similar in both groups [3]. Moreover, a subsequent large prospective study compared SBP reduction to 110–139 versus 140–179 showed more renal adverse events in intensive blood pressure reduction group [54]. A recent meta-analysis that included 4360 patients from 5 randomized clinical trials (RCTs) showed that intensive blood pressure reduction was associated with a trend for lower risk of significant ICH expansion compared with standard treatment (OR, 0.82; 95% CI, 0.68 to 1.00, $p = 0.056$), especially in larger RCTs [6].

Besides blood pressure control, patients with intratumoral hemorrhage who have excessive vasogenic edema should be treated with steroids (e.g., dexamethasone) in order to reduce the mass effect [48]. Elevated intracranial pressure (ICP), which might be life-threatening, is not uncommon especially in large hemorrhages. Emergent therapy for increased ICP was administered to 13% of cancer patients with ICH in one study [48]. Raising the head of bed to 30–45° with maintaining midline head and neck position is the first step in high ICP management. Sedation and pain control (e.g., propofol or midazolam and fentanyl infusions) are essential. Osmotherapy with intravenous mannitol or hypertonic saline is frequently required. Neuromuscular paralysis, hyperventilation (which is a temporary measure), and even barbiturate coma are sometimes unavoidable in order to control ICP [22].

Seizures should be treated using antiepileptic medications [26]. Choosing among different agents depends on other comorbidities, particularly renal and hepatological functions. Status epilepticus is a neurocritical emergency that need to be managed according to current guidelines [7]. Any otherwise unexplained change in mental status has to trigger a continuous video electroencephalography (cvEEG) monitoring to evaluate for subclinical seizures, especially if repeated neuroimaging is stable and ICP is under control. If electrographic seizures are found, they have to be treated with anti-seizure drugs [26].

Patients with ICH should have intermittent pneumatic compression for prevention of venous thromboembolism (VTE) beginning the day of hospital admission. After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered for prevention of VTE in patients with lack of mobility after 1–4 days from onset. Glucose should be monitored. Both hyperglycemia and hypoglycemia should be avoided. In all patients, a formal screening procedure for dysphagia should be performed before the initiation of oral intake to reduce the risk of pneumonia [26].

The management of acute SDH and EDH in patients with cancer is pretty much the same as in general population [66]. Small (less than 10 mm clot thickness) acute SDH without evidence of elevated intracranial pressure or severe neurological deficits can be managed conservatively without a surgical intervention [16]. Similarly, small and asymptomatic chronic SDH can be managed with observation [19]. On the other hand, surgery is required in large and/or symptomatic SDH, whether acute or chronic [16, 19].

Patients with cancer who develop acute SAH from saccular cerebral aneurysms should be treated according to current guidelines [13]. The ruptured aneurysm should be secured with endovascular coiling or surgical clipping (depending on its characteristics) as early as feasible to reduce the rate of rebleeding. Between the time of SAH symptom onset and aneurysm obliteration, blood pressure should be controlled with a titratable agent to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure. For patients with an unavoidable delay in obliteration of aneurysm, a significant risk of rebleeding, and no compelling medical contraindications, short-term (72 h) therapy with tranexamic acid or aminocaproic acid is reasonable to reduce the risk of early aneurysm rebleeding [13]. Oral nimodipine should be administered to all patients with aneurysmal SAH as it has been shown to improve neurological outcomes.

Aneurysmal SAH is not a simple disease as many complications can come with it. When acute symptomatic hydrocephalus occurs, it

should be managed by cerebrospinal fluid (CSF) diversion, either with external ventricular drain (EVD) or lumbar drainage, depending on the clinical scenario. Delayed cerebral ischemia (DCI) occurs in about 30% of patients with aneurysmal SAH, usually between 4 and 14 days after the onset of symptoms. DCI is defined as any neurologic deterioration (focal or global) presumed secondary to cerebral ischemia that persists for more than 1 h and cannot be explained by any other neurologic or systemic condition [62]. Maintenance of euvolemia and normal circulating blood volume is recommended to prevent DCI. In case it happens, induction of hypertension is recommended unless blood pressure is elevated at baseline or cardiac status precludes it. Cerebral angioplasty and/or selective intra-arterial vasodilator therapy is reasonable in patients with symptomatic cerebral vasospasm, particularly those who are not rapidly responding to hypertensive therapy [13]. Hyponatremia is seen often in patients with aneurysmal SAH. Fludrocortisone acetate and hypertonic saline solution are used for correcting sodium levels. Finally, heparin-induced thrombocytopenia (HIT) and deep venous thrombosis are relatively frequent complications after aneurysmal SAH. Early identification and targeted treatment are recommended, but further research is needed to identify the ideal screening paradigms [13].

It is worth mentioning that, in cancer patients, SAH might be related to mycotic, and in exceptional cases neoplastic, aneurysms [49, 66]. Those types of aneurysms are not easily amenable to surgery or endovascular coiling. Antibiotics are the mainstay of mycotic aneurysm-related SAH management, whereas radiation and chemotherapy are therapeutic options in case of neoplastic aneurysms [66].

As mentioned earlier in this chapter, bleeding diathesis is a major risk for ICH, and frequently it is the underlying etiology, especially in cancer patients. When ICH occurs in the setting of bleeding diathesis, treatment should be directed toward correcting the coagulopathy. If thrombocytopenia exists, platelet transfusions should be administered with a goal platelet value of more than 50,000–70,000/mm³ [48, 66]. On the other

hand, the usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is uncertain [26]. Patients with elevated prothrombin or partial thromboplastin times should be treated with intravenous vitamin K and fresh frozen plasma (FFP). In addition, an underlying etiology such as sepsis need to be treated in case of DIC [66].

Obviously, anticoagulation medications must be held in the setting of acute ICH. Patients who are receiving heparin should be given protamine sulfate as soon as possible. Antivitamin K agents (i.e., warfarin) need to be reversed. Intravenous vitamin K should be administered in all cases. Although FFP has been given frequently, prothrombin complex concentrate (PCC) may have fewer complications and correct the INR more rapidly than FFP. PCC might be considered over FFP according to the most recent ICH guidelines [26]. Importantly, the administration of rFVIIa is not recommended because it does not supply other vitamin K-dependent coagulation factors and does not improve survival or functional outcomes in patients with ICH [41].

As direct oral anticoagulants (DOAC) are being prescribed more, ICH in their presence is increasingly encountered. Specific reversal agents for management of serious hemorrhage in patients taking DOAC are being developed. Idarucizumab is a humanized monoclonal antibody fragment for dabigatran and is already approved by the FDA for the treatment of dabigatran-induced major hemorrhage [52]. Andexanet is a recombinant factor Xa protein without catalytic activity that captures circulating factor Xa inhibitors (e.g., rivaroxaban or apixaban). A multicenter, prospective, open-label, single-group study is ongoing to evaluate the safety and efficacy of andexanet, with promising preliminary results already published [14].

Non-pharmacologic

There is an important role for surgery in the management of ICH in cancer patients, depending on the location of the bleeding and the clinical status. Patients with cerebellar hemorrhage who are deteriorating neurologically or who have

brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible [17, 26].

In supratentorial hemorrhages, the underlying tumor should be considered for resection if surgically feasible [36, 58]. The presence of a brain neoplasm (whether primary or metastatic) was an exclusion criterion in the major clinical trials of surgical interventions in supratentorial ICH [44, 45], and subsequently their results cannot be applied in such cases. However, those trials can still be valid when ICH occurs in patients with systemic cancers who do not have known intracranial involvement. In STICH trial, surgical removal of supratentorial ICH did not improve functional outcomes [44]. Similar results were found in STICH II trial which included ICH patients with lobar locations only [44]. Of note, in both trials craniotomy was used in the vast majority of cases in order to remove the clot. On the other hand, MISTIE III is an ongoing large clinical trial aims to evaluate how a minimally invasive surgical approach of clot removal (using surgical aspiration followed by alteplase clot irrigation) can impact functional outcomes in supratentorial ICH [1].

Acute hydrocephalus can result from CSF outflow obstruction or intraventricular hemorrhage. An external ventricular drainage (EVD) should be placed in those situations, and it might be life-saving [36]. It is worth mentioning that administering intrathecal alteplase through EVD in cases of IVH that is obstructing third and/or fourth ventricles was evaluated in a large clinical trial (CLEAR III) [25]. Although it was safe, intrathecal alteplase did not improve functional outcomes.

Whole-brain radiation may be considered in patients with unresectable tumors or those with more than three metastatic lesions as a palliative measure [66]. In a retrospective study of cancer patients with ICH, 23% of them ultimately treated with cranial irradiation [48].

In patients with hyperleukocytosis (e.g., in acute myeloid leukemia), leukapheresis prior to chemotherapy initiation was suggested as a preventive measure in order to reduce the

incidence of ICH [9, 70]. However, the data is conflicting. Furthermore, there is no evidence of any long-term survival benefit from this practice [9, 12].

Management Algorithm

ICH is suspected (acute onset of mental status change, headaches, or focal neurological deficit)

↓

Evaluate airway, breathing, and circulation (ABC)

↓

Obtain STAT CT head without contrast

↓ (If ICH is found)

Consult neurology and neurosurgery

Evaluate for coagulopathy (check CBC and coagulopathy panel, check for current anticoagulation medications use) → correct accordingly, reverse anticoagulation medication effect

Control blood pressure using intravenous agents (e.g., nicardipine infusion) for SBP goal of <140

If vasogenic edema is found → start steroids (e.g., dexamethasone)

↓

Admit to ICU (preferably NeuroICU)

Prognosis

Patients with cancer who suffer an intracranial hemorrhage have worse clinical outcomes than patients who develop ICH without a history of cancer [47]. From a large specimen of the Nationwide Inpatient Sample, Murphy et al. retrospectively compared outcomes in ICH patients with and without history of systemic cancer. In multivariate logistic regression analysis adjusted for demographics, comorbidities, and hospital-level characteristics, patients with cancer had higher odds of death (OR 1.62, 95% CI 1.56–1.69) and lower odds of favorable discharge (i.e., home or rehab) (OR 0.59, 95% CI 0.56–0.63) than patients without cancer. In this study, patients with cancer were more often diagnosed with coagulopathy than patients without cancer (14.1% vs. 5.4%, $P < 0.001$), a fact that

would, at least partially, explain the difference in outcomes as coagulopathy is well-known to be a predictor for hematoma expansion and poor prognosis in ICH patients [8, 21]. Moreover, cancer patients with ICH probably were managed less aggressively comparing to ICH patients without history of cancer, as the latter had more procedures done according to medical records in Murthy's study [47].

Cancer subtype may influence outcomes after ICH. Patients with nonmetastatic hematologic tumors and those with metastatic disease had worse outcomes than patients with nonmetastatic solid tumors. Interestingly, the rates of coagulopathy were higher in patients with nonmetastatic hematologic tumors (26.4%) and those with metastatic solid or hematologic tumors (16.5%) comparing to patients with nonmetastatic solid tumors (6.3%) [47]. In another study, Navi et al. found that patients with solid tumors had the best functional outcome at discharge, with 53% being completely or partially independent, compared with 44% of patients with primary brain tumors and 30% of patients with hematologic tumors [48].

Predictors of poor prognosis in patients with cancer and ICH include an underlying systemic malignancy (i.e., not a primary brain tumor), multiple hemorrhagic foci, hydrocephalus, treatment for increased intracranial pressure (likely reflects more severe disease), and the absence of ventriculostomy [48].

Mortality rates were the highest in patients with hematopoietic tumors (36% during hospitalization), whereas patients with primary brain tumors (8%) had the lowest. Thirty-day mortality was 31%, and 1-year mortality was 78% for the entire cohort. Median survival was 5.9 months for patients with primary brain tumors, 2.1 months for patients with solid tumors, and 1.5 months for patients with hematologic tumors [48].

In Navi's study, the multivariate models showed that impaired consciousness, not having a primary brain tumor, multiple foci of hemorrhage, hydrocephalus, increased ICP treatment, and not receiving ventriculostomy were significant predictors of 30-day mortality. All of these

variables, except not having a primary brain tumor, were also independently predictive of 90-day mortality. Additionally, hemiparesis and current chemotherapy were significant predictors of mortality at 90 but not 30 days via multivariate analysis. Interestingly, neither anticoagulant nor antiplatelet use was a significant predictor of poor prognosis or mortality [48].

Conclusion

Intracranial hemorrhage is associated with high rates of morbidity and mortality, and it is encountered frequently in cancer patients. The most common etiologies in this population are intratumoral hemorrhage and coagulopathy. As the majority of patients are symptomatic, establishing the diagnosis with a CT scan as quickly as possible is vital. Most patients require an admission to a neurological intensive care unit and a neurosurgical consultation is almost always needed. Medical management is necessary, and, at times, surgical interventions might be life saving. Overall, clinical outcomes of intracranial hemorrhage remain poor, especially in cancer patients.

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