Neoplasm-related Sudden Death: Causes and Clinicopathological Characteristics

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Abstract

Patients with neoplastic diseases, especially malignancies, are at greatly elevated risk of sudden death, because they may suffer from a variety of neoplasm-, and/or treatment-related clinical conditions including myelosuppression, immunosuppression, coagulation abnormalities, metabolic disorders, and malnutrition. Cancer patients die suddenly of miscellaneous etiologies, and about one third of sudden death in cancer patients is attributed to neoplasm-related complications.

In the literature, the majority of neoplasm-related sudden deaths (NSDs) are caused by neoplasms affecting critical organs such as the heart and brain. In addition, neoplasms damaging respiratory system or causing acute blood loss are responsible for sudden death. Mechanisms are miscellaneous and most are directly related to the anatomical location of the neoplasm. On the other hand, regardless of the site, specific types of neoplasm (e.g. hormone-producing tumors) sometimes cause sudden death by mechanisms which a pathophysiological function peculiar to the tumor induces critical manifestations of vital organs such as the heart.

As mentioned above, causes of NSD is classified as follows; (1) cardiac tumors, (2) brain tumors, (3) pulmonary tumor embolism, (4) asphyxia, (5) massive exsanguinations, and (6) sudden death due to neoplasm-specific pathophysiology. The latter includes amyloidosis, hyperviscosity syndrome, and hormone-induced complications, and these diseases can present with a variety of lethal clinical manifestations. In this chapter,
clinical and pathological characteristics of NSDs are described based on this classification with a review of the literature.

**Introduction**

Patients with neoplastic diseases, especially malignancies, are at greatly elevated risk of sudden death, because they may suffer from a variety of neoplasm-, and/or treatment-related clinical conditions including myelosuppression, immunosuppression, coagulation abnormalities, metabolic disorders, and malnutrition. Cancer patients die suddenly of miscellaneous etiologies, and about one third of sudden death in cancer patients is attributed to neoplasm-related complications [1].

The cardiovascular and central nervous systems are crucial for life, and any damage affecting them can be life-threatening. In the literature, the majority of neoplasm-related sudden deaths (NSDs) are caused by neoplasms affecting critical organs such as the heart and brain. In addition, neoplasms damaging respiratory system or causing acute blood loss are responsible for sudden death. Mechanisms are miscellaneous and most are directly related to the anatomical location of the neoplasm. On the other hand, regardless of the site, specific types of neoplasm (e.g. hormone-producing tumors) sometimes cause sudden death by mechanisms which a pathophysiological function peculiar to the tumor induces critical manifestations of vital organs such as the heart.

An etiological classification of NSD is presented in Table 1. In this chapter, clinical and pathological characteristics of NSDs are described following this classification with a review of the literature.

**Table 1. Etiological Classification of Neoplasm-Related Sudden Death**

1) Cardiac tumors  
2) Brain tumors  
3) Pulmonary tumor embolism  
4) Asphyxia  
5) Massive exsanguination  
6) Sudden death due to neoplasm-specific pathophysiology  
   a) Amyloidosis  
   b) Hyperviscosity syndrome  
   c) Hormone-induced complications

**1. Cardiac Tumors**

Cardiac tumors, regardless of their nature (i.e., primary or metastatic, benign or malignant) constitute risks for sudden death by themselves. The pathophysiology is
miscellaneous, including cardiac ischemia, arrhythmia, pump failure, outflow obstruction, valvular dysfunction, and cardiac tamponade.

1.1. Primary Cardiac Tumors

In the literature, there have been a large number of cases of sudden death attributed to primary cardiac neoplasms. Cina et al. [2], in their review, indicated that in most cases the tumors are histologically benign but their intracardiac location precipitates conductive and hemodynamic abnormalities.

1.1.1. Cystic Tumor of the Atrioventricular (AV) Node

The cystic tumor of the AV node is a benign, congenital, cystic mass located at the base of the atrial septum. The size ranges from 2 to 20 mm [3], and microscopically ductular structures, cysts, and solid nests of epithelial-like cells within loose fibrous stroma are characteristic (Figure 1). Occasionally, cysts are filled with proteinaceous debris. Previously the cystic tumor of the AV node was regarded as a mesothelioma, but it is now considered to be a developmental abnormality of epithelial nature and endodermal origin [4, 5]. It is well known as a cause of AV block or sudden death [5,6], and has been called the “smallest tumor causing sudden death” [7]. In fact, this tumor is the most common neoplasm of cardiac origin that causes sudden death [2]. Since the gross findings may be minimal, a lesion may not be discovered unless the AV node is microscopically examined [2]. Therefore, a histopathological examination of AV node is essential in order to clarify the etiology of cardiac sudden death.

![Figure 1](image1.jpg)

Figure 1. Microscopic findings of a cystic tumor of the atrioventricular (AV) node. **A** The tumor (T) is located in the lower right atrium (RA) and has reached to the AV node (N). (IVS: interventricular septum) (Azan stain). **B** Multiple microcysts lined by columnar and cuboidal cells are apparent within loose fibrous stroma (hematoxylin-eosin). (Courtesy by Dr. Tomio Arai, Tokyo Metropolitan Geriatric Hospital).
1.1.2. Fibroma

Fibroma, the most commonly resected cardiac tumor of children, constitutes the second most frequent causing sudden death [2]. The cardiac sites of fibromas are, in order of decreasing frequency, the interventricular septum, left ventricular free wall, right ventricle, and atria [3].

The location has been noted as a determining factor in the presentation and outcome of affected patients. Fibromas arising in the interventricular septum are inoperable, but those of the ventricular free wall may be removed surgically.

It seems that sudden death occurs due to compression of the conducting system (bundle of His) or triggering of ventricular fibrillation. In one study [8], more than half of the cases presenting with sudden death had tumors in the interventricular septum, where compression of the conduction system is more likely.

1.1.3. Myxoma

Among primary cardiac tumors, myxoma is the most common in adults and is the third most frequent neoplasm causing sudden death [2].

It usually develops in the atria; about 75% originate in the left atrium, and 15 to 20% in the right atrium.

If the tumor is sufficiently large, soft, and easily deformable, and if it has a long stalk, obstruction of the orifice of the mitral or tricuspid valve may occur [9]. Sudden death may be the result of either acute disturbance in cardiac hemodynamics or systemic embolization by tumor fragments.

The lethal potential of this tumor can be attributed to both its location (usually in the left atrium) and its configuration [2].

1.1.4. Rhabdomyoma

Rhabdomyoma is the most common primary cardiac tumor in children. It may occur as solitary, multiple or diffuse lesions of the myocardium, and is considered to be a malformation tumor (hamartoma), rather than a true neoplasm [10]. Sudden cardiac death may result from rhythm disturbance, outflow obstruction and valvular distortion [11]. Cardiac rhabdomyoma is also frequently associated with tuberous sclerosis, an autosomal dominant inherited disease.

If a cardiac rhabdomyoma is identified in patients presenting with sudden death, other lesions characteristic of this syndrome such as adrenal angiomyolipoma and subependymal giant cell astrocytoma, may further be present and mortality may in fact be due to complications of tuberous sclerosis [2, 11-13].

1.1.5. Papillary Fibroelastoma

The papillary fibroelastoma is a benign endocardial papilloma predominantly affecting the cardiac valves, especially the aortic valve (Figure 2), where it has been implicated in sudden death because of obstruction of the ostium of the right or left coronary artery. In one review of reported cases of papillary fibroelastoma [14], sudden death was found in 21 of 725 patients (2.9%).
Figure 2. Papillary fibroelastoma of the aortic valve. A) Macroscopically, an exophytic tumor with thin stalk, measuring 5 mm in diameter, is apparent on the right coronary cusp of the aortic valve (arrow). B) Microscopic examination shows a papillary endocardial tumor with hyalinized central core. Fibrin clot and bacterial colonization are also evident. (hematoxylin-eosin, original magnification x40).

1.1.6. Hemangioma
Hemangiomas are proliferations of endothelial cells forming vascular channels of variable size. The cardiac hemangioma occurs in patients of all ages and there is a male predominance [15]. It appears most lethal when disrupting the conducting system or involving the atrioventricular node. Very rarely, this tumor can induce cardiac tamponade resulting in sudden death [16, 17].

1.1.7. Angiosarcoma
Angiosarcoma is the most frequent primary malignant cardiac neoplasm and most commonly arises in the right atrium [18]. Extension into the pericardial sac or atrial chamber often leads to hemopericardium, cardiac tamponade, or obstruction of blood flow. Widespread metastasis (especially pulmonary) is common and may be related to causes of death [19]. However, the number of patients with cardiac angiosarcoma presenting with sudden death is limited [2, 20, 21].

1.1.8. Miscellaneous Primary Cardiac Tumors
Many other kinds of primary cardiac tumors have been reported as causes of sudden death, although their incidences are very low. They include the rhabdomyosarcoma, malignant lymphoma, undifferentiated sarcoma, fibrosarcoma, malignant nerve sheath tumor, teratoma, lipoma, angiomyloma, cardiac inflammatory myofibroblastic tumor, low-grade myofibroblastic sarcoma, and coronary artery intimal sarcoma [2, 22-25].

1.2. Metastatic Cardiac Tumors
Metastatic tumors in the heart are far more frequent than primary neoplasms, by at least a 30 to 1 ratio [26]. The most common lesions with cardiac metastatic potential are carcinomas of the lung, breast, esophagus and thyroid gland, leukemia and malignant lymphomas [27]. Metastatic cardiac tumors also cause sudden death due to impaired cardiac function, including
cardiac tamponade, conduction disturbance and outflow obstruction [28-30]. In the literature, metastatic cardiac tumors responsible for sudden death have been derived from a variety of organs, such as the lung [30], esophagus [31], thyroid gland [32], pancreas [33] and colon [28], as well as soft tissue [34]. T-cell lymphomas, when compared with B-cell lymphomas, metastasize more frequently and are more likely to give rise to cardiac manifestations, including sudden death (Figure 3) [35].

![Figure 3. An example of cardiac involvement by malignant lymphoma in a 74 year-old man presenting with sudden death. Note diffuse interstitial infiltration of lymphoma cells (hematoxylin-eosin, original magnification x200).](image)

2. Brain Tumors

Brain tumors, like cardiac tumors, are etiological factors for NSD. Although the actual proportion of sudden deaths from this cause is very low (0.02% to 2.1%) [36], many anecdotal cases have been reported. Any kind of brain tumors, regardless of their nature (i.e. primary or metastatic, benign or malignant), can cause sudden death. In the literature, however, the astrocytoma-glioblastoma category has predominated [37]. Other examples include oligodendroglialoma, medulloblastoma, subependymoma, microglioma, meningioma, colloid cyst, lymphoma, teratoma, hemangiopericytoma and metastatic brain tumors [37-45]. Of the metastatic intracranial tumors, bronchial carcinoma, choriocarcinoma and melanoma are the most common [46].

Sudden death in patients with brain tumors is caused mainly by rapid functional deterioration of a vital focus, such as the brainstem, which controls circulatory or respiratory functions. Mechanisms of sudden death have been explained as detailed below.

2.1. Raised Intracranial Pressure

The most common mechanism is raised intracranial pressure as a result of an intracranial expanding (space-occupying) lesion. Hemorrhage from a tumor often causes rapid increase of the tumor mass. Raised intracranial pressure finally causes cerebral herniation and brainstem compression with a fatal outcome.
2.2. Acute Obstructive Hydrocephalus

Tumors that can obstruct cerebrospinal fluid flow are responsible for acute hydrocephalus. It is the site of tumor, rather than its nature, that is of importance. If there is a small tumor in a crucial site adjacent to a ventricular foramen, then it is of much greater importance than a large expanding tumor in a frontal or occipital lobe. For example, tumors of the third ventricle can cause acute obstructive hydrocephalus by blocking the foramen of Munro or the posterior third ventricle and cerebral aqueduct. Primary third-ventricle tumors include colloid cysts (the most frequent type), astrocytomas, ependymomas, and choroid plexus papillomas, and these tumors have been reported as causes of sudden death [47]. Leptomeningeal seeding of tumor cells, such as lymphoma cells, may also be responsible for acute obstructive hydrocephalus [48]. Most patients with acute hydrocephalus are not diagnosed antemortem as having brain tumors, because clinical manifestations of acute hydrocephalus, including vomiting, headache and lethargy, often lead to a misdiagnosis as a viral illness such as gastroenteritis [47].

2.3. Neoplastic Involvement of the Respiratory and/or Cardiac Centers

In infratentorial tumors, direct involvement with the respiratory and/or cardiac centers in the brainstem can cause sudden death. In the literature, oligodendroglioma [42,43], ganglioglioma [49,50], and mycosis fungoides [51] have been reported as responsible lesions. Mechanical compression, without direct invasion, caused by tumors neighboring the brainstem may be involved [39].

2.4. Epilepsy

The incidence of epileptic seizures for all intracranial tumors is about 20-50%, but sudden death caused by epilepsy is rare [52]. In one review article [52], tumors causing fatal epilepsy were miscellaneous, including low-grade astrocytoma, anaplastic astrocytoma, oligodendroglioma, meningioma, subependymal giant cell astrocytoma, anaplastic oligodendroglioma, gangliocytoma, ependymoma, subependymoma, and teratoma. The most common localization was the frontal lobe and the thalamus. It is interesting that there was no tumor solely in the parietal lobe, which is reported to be the most common location for tumors causing seizures. The mechanism of epilepsy-induced sudden death remains controversial. The most widely accepted theory proposes that seizure activity results in autonomic nervous system discharge, which ultimately triggers lethal cardiac arrhythmias or respiratory arrest [12, 52].

2.5. Neurogenic Pulmonary Edema

Some patients with brain tumor die suddenly of neurogenic pulmonary edema [45]. Not only brain tumors but also subarachnoid and intraventricular hemorrhage may be responsible.
The exact pathophysiology is unclear, but it may feature an adrenergic response induced by cerebral insult, which leads to increased pulmonary hydrostatic pressure and lung capillary permeability. It is known that an increase of cerebrospinal fluid pressure, infusion of thrombin and fibrinogen into the cistern magna, and intravenous or intrathecal infusion of massive amounts of catecholamines can cause neurogenic pulmonary edema [45].

3. Pulmonary Tumor Embolism

Autopsy studies estimate that the incidence of pulmonary tumor embolism (PTE) is between 3% and 26% among patients with solid tumors. Primary tumors for PTE have been reported to be, in order of decreasing frequency, carcinomas of the breast, stomach, lung, liver, prostate, and pancreas [53]. Pulmonary hypertension due to PTE is considered a major contributory cause of death, which may occur in as much as 8% of cases [54]. Although comprehensive studies are still lacking, many anecdotal case reports dealing with PTE-induced sudden death have been published. Sudden deaths are caused by tumors that have high angioinvasive potential, such as renal cell carcinomas (Figure 4) [1], hepatocellular carcinomas [55], testicular germ cell tumors [56], and Wilms tumors [57,58]. Primary tumors causing PTE are often undiagnosed before sudden death, which is the first clinical presentation in many cases. Tumors originating from the vessel wall of large veins or pulmonary artery can also obstruct the pulmonary arterial system and cause mortality, for example with leiomyosarcoma of the pulmonary artery [59] and intravenous leiomyoma [60]. Strictly speaking, when tumors in the pulmonary artery are contiguous with the original tumor site, they are not “PTE” because PTE is defined as “the presence of isolated cells or clusters of tumor cells within the pulmonary arterial system, which are not contiguous with primary or metastatic foci” [61]. However, because these types of tumors can cause sudden death by the same mechanism as true “PTE”, it may be reasonable to describe here as “sudden death due to tumorous obstruction of the pulmonary circulation system.”

![Figure 4](image)

Figure 4. Microscopic findings of a neoplastic pulmonary embolus from a renal cell carcinoma in a 54-year-old man. The pulmonary artery (PA) is occupied by tumor cells (T). A small amount of thrombus is also observed. (hematoxylin-eosin (A) and elastic van Gieson stain (B), original magnification x40). This patient was found in the state of cardiopulmonary arrest. Neoplastic involvement of the right renal vein, inferior vena cava, right atrium, and pulmonary truncus was grossly observed.
3.1. Pulmonary Tumor Thrombotic Microangiopathy

Recently, a distinct form of PTE, designated as “pulmonary tumor thrombotic microangiopathy (PTTM)”, has become recognized as a cause of sudden death.

Clinicopathological characteristics of PTTM are quite different from those of conventional PTE in many points, therefore it seems better to document PTTM as a single disease entity. PTTM is in fact a rare clinicopathologic condition that causes severe clinical manifestations including pulmonary hypertension, right-sided heart failure and sudden death. It is characterized by widespread tumor emboli in the small arteries and arterioles of the lung, associated with thrombus formation and fibrocellular and fibromuscular intimal proliferation [62]. It differs from conventional PTE in that metastatic tumors do not cause simple mechanical obstruction of the pulmonary vasculature but rather stimulate vessel reactions (Figure 5). Apparent clinicopathologic features [63,64] include:

1) adenocarcinomas as the predominant histology, especially of poorly differentiated type including the signet-ring cell carcinoma;
2) the stomach as the most frequent primary site, PTTM often being due to clinically undetected, occult gastric carcinoma;
3) no age dependence, both the old and young being affected; and
4) a difficult antemortem diagnosis with frequent misdiagnosis as primary pulmonary hypertension.

In cases of sudden death with unexplained pulmonary hypertension or cor pulmonale, the possibility of PTTM should be considered and special attention should be paid in postmortem examination. Since gross findings of the lung are often unremarkable, microscopic examination of the lung is required for the diagnosis. Although neoplasms of various organs can cause PTTM [65], the most frequent neoplasm is, as mentioned above, the gastric carcinoma [62]. Therefore, in cases of PTTM with obscure primary neoplasm, the stomach should be examined carefully. Many serial step sections of the stomach may be necessary for detection of the primary lesion because PTTM is sometimes caused by a tiny early cancer limited to the mucosal or submucosal layer [66, 67].
Figure 5. Histologic findings of pulmonary tumor thrombotic microangiopathy (PTTM) in a 62-year-old male patient with gastric cancer, who died suddenly of pulmonary hypertension. A) Characteristic findings of PTTM showing a tumor embolism associated with thrombus formation and fibrocellular intimal proliferation in a small pulmonary artery (hematoxylin-eosin, original magnification x40). B) A small pulmonary artery is occluded by proliferated intima and cancer cells. A small amount of fibrin thrombus is also apparent (hematoxylin-eosin, original magnification x100). C) Complete vascular occlusion of a small pulmonary artery due to fibrocellular intimal proliferation. Note that no tumor cells are identifiable within this arterial lesion (hematoxylin-eosin, original magnification x100).

4. Asphyxia

Asphyxia is one mechanism of NSD. Neoplasms affecting the upper airway can cause lethal airway obstruction. In the literature, lesions arising in the larynx causing sudden death include schwannoma [68], lymphoma [69], papillomatosis [70, 71], basosquamous carcinoma [72], and hemangioma [73]. Prolapsed tumors originating from the esophagus (fibrolipoma) [74] or hypopharynx (lipoma) [75] are also reported causes. In addition, lethal asphyxia may occur as a result of external compression of the trachea or bronchus caused by mediastinal tumors such as lymphoma [76], paraganglioma [77], and esophageal leiomyoma [78].

5. Massive Exsanguination

Massive exsanguination can be a lethal complication in neoplastic diseases. The anatomical environment around neoplasms is very important in this context and neoplasms in the body cavity may cause hemoperitoneum or hemothorax. Examples originating from or neighboring great vessels present an obvious risk for vessel rupture.

5.1. Hemoperitoneum

Intraperitoneal bleeding is a common etiology for massive exsanguination. Hemoperitoneum due to spontaneous hepatic rupture is a well-known fatal complication of
hepatocellular carcinoma (Figure 6), with a reported incidence of 3% [79]. Metastatic liver tumors can also cause spontaneous rupture [80]. Extrahepatic neoplasms causing hemoperitoneum and sudden death include mesenteric malignant hemangioendothelioma [81], Wilms tumor [76] and chronic myelogenous leukemia with splenic rupture [82]. Even a uterine leiomyoma, a very common benign neoplasm, can be a cause of fatal intraperitoneal bleeding [13].

![Image of a case of sudden death in a 77-year-old man with hepatocellular carcinoma. Autopsy reveals a protruding tumor (T), measuring 6.5 x 5.0 x 4.0 cm, of the left lobe of the liver (L). The tumor has ruptured and was associated with 2000 mL of hemoperitoneum. (GB; gallbladder, S; stomach)](image)

Figure 6. A case of sudden death in a 77-year-old man with hepatocellular carcinoma. Autopsy reveals a protruding tumor (T), measuring 6.5 x 5.0 x 4.0 cm, of the left lobe of the liver (L). The tumor has ruptured and was associated with 2000 mL of hemoperitoneum. (GB; gallbladder, S; stomach)

5.2. Hemothorax

Intrapleural bleeding from tumors may also cause massive exsanguination and the negative pressure in the intrapleural cavity may exacerbate bleeding from a pleural tumor. Many lethal cases have been documented with hepatocellular carcinomas [83]. In von Recklinghausen’s disease or neurofibromatosis, bleeding in the pleural cavity has been reported as a result of rupture of friable vasculature by either vascular invasion or arterial dysplasia [84, 85].

5.3. Alimentary Tract Hemorrhage

Alimentary tract hemorrhage is another cause of massive exsanguination. Rupture of esophageal varices often induces sudden death in patients with hepatocellular carcinoma and liver cirrhosis [86]. Fistula formation caused by tumor invasion between great vessels and the alimentary canal may also be responsible for fatal blood loss (Figure 7) [1].
5.4. Bleeding from Superficial Vessels

Primary and metastatic tumors existing in the subcutaneous tissue may invade large vessels, such as the femoral artery, and destroy the vessel wall, leading to fatal bleeding [87].

6. Sudden Death Due to Neoplasm-Specific Pathophysiology

Specific types of neoplasm sometimes cause sudden death by mechanisms which pathophysiological function peculiar to the neoplasm induces critical manifestation of vital organs.

6.1. Amyloidosis

Amyloidosis sometimes occurs as a complication of some neoplastic diseases, including multiple myeloma and thyroid medullary carcinoma. The heart is one of the target organs for amyloid deposits and cardiac amyloidosis can cause lethal arrhythmia and/or pump failure leading to sudden death [88]. Another mechanism of amyloidosis-induced sudden death is hepatic or splenic rupture as a result of amyloid deposition in these organs [89].
6.2. Hyperviscosity Syndrome

The hyperviscosity syndrome is one of the lethal complications in patients with hematological malignancies. Embolic events due to hyperviscosity have been documented as a cause of sudden death in multiple myeloma [90] and leukemia [76].

6.3. Hormone-Induced Complications

6.3.1. Hypercalcemia

Hypercalcemia is one critical complication in cancer patients. Metastatic bone tumors destroy bony structures and induce hypercalcemia. In addition, over-production of parathyroid hormone (PTH) or PTH-related peptide (PTH-rP) by specific types of neoplasm can cause a lethal clinical condition as a result of hypercalcemia. Adult T-cell leukemia/lymphoma (ATLL) is a well-known malignancy inducing lethal hypercalcemia. Metastatic calcification of the heart is reported as a cause of sudden death in patients with ATLL [91] and parathyroid adenoma [92].

6.3.2. Hypokalemia

Hypokalemia may cause severe clinical symptoms such as cardiac arrhythmia and respiratory failure due to muscle weakness. Hypokalemia and consequent lethal arrhythmia are documented to constitute a fatal pathophysiology in patients with primary aldosteronism [93] and Cushing syndrome [94].

6.3.3. Pheochromocytoma

Pheochromocytoma can cause miscellaneous severe clinical symptoms. In addition to critical arterial hypertension, severe cardiac arrhythmia must be recognized as a life-threatening associated complication [95-97]. Catecholamine-induced cardiomyopathy due to pheochromocytoma may also elevate the risk of cardiac sudden death [98].

6.3.4. Insulinoma

Hypoglycemia is itself a lethal clinical condition, and increased sympathetic nerve activity followed by hypoglycemia can be responsible for lethal cardiac arrhythmia. In the literature, sudden death due to hypoglycemia-induced cardiac arrhythmia has been reported in a patient with a duodenal insulinoma [99].

References


