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The Confused Oncologic Patient: A Rational Clinical Approach

Craig Nolan, M.D and Lisa M. DeAngelis, M.D

Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, New York 10065

Abstract

Purpose of review—The purpose of this review is to provide a practical clinical approach to confusion in the patient with cancer. Confusion in the cancer population has a broader differential diagnosis than in the general medical population. The clinician must consider the usual differential diagnoses as well as causes unique to the cancer patient including direct complications from the cancer and indirect complications related to cancer treatment.

Recent findings—In the recent age of precision medicine, the oncologist now utilizes the genomic profile of both the patient and the tumor to provide advanced biologic therapies including targeted anticancer drugs, antiangiogenic agents, and immunotherapy. Such advances carry with them an emerging pattern of neurotoxicity which, although less well described in the literature, is now an important consideration to the clinical approach to confusion in cancer patients.

Summary—Confusion is the most common neurologic complication in cancer and is associated with significant morbidity, mortality, and prolonged hospital stays resulting in increased health care costs. Early recognition and treatment of delirium is essential to improve clinical outcomes.

Keywords

Encephalopathy in cancer; reversible delirium; precision medicine

Introduction

In 2016, the American Society of Clinical Oncology (ASCO) reported that 1.7 million Americans were diagnosed with cancer in the year 2015 and that this number will rise to 2.3 million in 2030.^{1,2} In this setting of increasing cancer rates, there has also been an explosion of new cancer therapies including: immune checkpoint inhibitors, T-cell therapies, tumor vaccines, antiangiogenic therapies, and various targeted agents, many of which cause frequent neurologic complications including confusion.^{3–7}

Confusion in the cancer patient is common.^{8–11} Multiple synonymous terms for confusion exist, including: encephalopathy, delirium, acute confusional state, reversible dementia, organic brain syndrome, and terminal restlessness referring to the agitated delirium often seen in the last days of life.¹² The incidence of confusion in cancer patients ranges from

Corresponding Author: Craig Nolan, M.D., Department of Neurology, Memorial Sloan-Kettering Cancer Center, 160 East 53rd Street, 2nd Floor, New York, New York 10022, Phone #: (212) 610-0527, Fax #: (929) 321-5016, nolan1@mskcc.org.

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57%–85 % compared to 15%–30% in medically ill hospitalized patients.^{13,14} In a prospective observational study of 352 cancer patients admitted to acute palliative care units (APCU) at the MD Anderson Cancer Center, delirium was the most common symptomatic complication occurring in 43% of patients at admission, and 70% during the entire APCU stay.¹⁵ In 2015, at Memorial Sloan Kettering Cancer Center (MSKCC), confusion or altered mental state accounted for 27% of all inpatient consultations requested of the Neurology service. This is a minimal incidence because it does not include the confused patients for whom a neurologic consultation was not called, those consulted by psychiatry, or those whose confusion was unrecognized.

Failure to recognize delirium in hospitalized patients is common, and may be due in part to the fluctuating nature of symptoms as well as failure to utilize proper tools for assessment and monitoring such as the Mini-Mental State Examination (MMSE) or Short Orientation Concentration Test (SOMCT). A retrospective review of 771 consecutive palliative care inpatient consults at a large cancer hospital found that 61% of delirium diagnoses were missed by the primary referring team and that hypoactive delirium was the most common subtype (63%).¹⁶ Given this high prevalence, cancer patients should be screened with an appropriate assessment on admission and throughout their hospital course.¹⁷ In the cancer patient hypoactive delirium due to hypoxia, infection, or metabolic encephalopathy is often missed and misinterpreted as fatigue, depression, or sedation from opioid pain medication. Cancer predominately affects individuals age 65 and older, and older age and a pre-existing psychiatric condition are associated with a missed diagnosis of delirium which is often misinterpreted as dementia in this population.^{16,18,19}

Delirium is associated with increased morbidity and mortality, prolonged hospital and intensive care unit (ICU) stays, as well as increased distress in patients, families, and caregivers.²⁰ To improve outcomes, the clinician must have a rational approach to the confused cancer patient, and Inouye's model of delirium is a good starting point.²¹ The clinician must recognize the predisposing risk factors for confusion (such as old age, dementia, mood disorder, substance abuse, hypoalbuminemia, cachexia, advanced cancer, bone metastases) and determine the more immediate precipitating factors which may be modifiable. Delirium is reversible in approximately 50% of cancer patients, and may require correction of only some and not all contributing causes.¹³ Frequently, multiple causes, a median of three in one series, are identified in patients with cancer.⁸ Confusion attributed to infection, electrolyte abnormalities, or medications is more likely reversible than when the delirium is the consequence of global hypoxic encephalopathy. The additional considerations in the confused cancer patient are those factors directly related to the cancer and its treatment.

Confusion: Direct Relation to Cancer

The differential diagnosis of confusion directly related to cancer is extensive and includes metabolic abnormalities, metastatic disease, vascular disorders, paraneoplastic and autoimmune syndromes, and inflammatory mediators (Table 1). The etiology is typically multifactorial. When a single cause for confusion is identified, it is usually structural such as multiple brain metastases, meningitis/encephalitis, or cerebral infarction. The clinical

evaluation should include a careful history to identify pre-existing risk factors and new interventions such as medications (Table 2). The neurologic examination may indicate lateralizing neurologic signs suggestive of brain metastases, signs of raised intracranial pressure such as papilledema, abducens nerve palsy indicating leptomeningeal metastasis (LM), or stupor from a global hypoxic-ischemic or metabolic encephalopathy. A complete laboratory evaluation is needed to assess for metabolic and immune conditions unique to cancer patients including tumor lysis syndrome (TLS), hypercalcemia of malignancy, cachexia/anorexia and paraneoplastic autoimmune syndromes (PNS/AIS).

Brain Metastases

Brain metastases (BM) occur in 10–30% of cancer patients and are most common in lung and breast carcinoma followed by melanoma.²² In a retrospective review of inpatients with BM over a 6 month period, 45.8% had cognitive changes.²³ Cognitive impairment is the initial complaint in approximately 30% of patients with BM, and often occurs with lateralizing signs. However, multiple small BM may cause confusion and personality change only. Some focal abnormalities such as an apraxia, aphasia, and abulia from metastases in the parietal or frontal lobes may be mistaken for confusion.

Worsening confusion in association with headache and disorientation is concerning for increased intracranial pressure potentially from vasogenic edema associated with BM or hydrocephalus from LM. In this setting, episodes of depressed consciousness, speech arrest, or loss of leg tone may occur and most likely represent plateau waves rather than seizure.

Tumor Lysis Syndrome

TLS occurs as the result of treatment-induced tumor cell death releasing intracellular potassium, phosphorus, and uric acid, causing hypocalcemia, hyperkalemia, and precipitating renal insufficiency or failure.^{24–27} Volume depletion and hematologic cancers associated with a high tumor burden are the major risk factors. Encephalopathy and seizures are common symptoms; prevention and treatment require aggressive hydration, urine alkalinization, and allopurinol or rasburicase to reduce urate levels.

Hypercalcemia of Malignancy

Hypercalcemia of malignancy occurs in 20% of patients with cancer, most commonly associated with multiple myeloma (MM), leukemia and non-Hodgkin lymphoma^{28,29} and among solid tumors, breast, lung, and renal cancer. Approximately 80% of cases are humoral, associated with parathyroid hormone-related protein (PTHrP) which increases bone resorption through osteoclast activation and osteoblast suppression.^{30,31} Less common causes are direct metastatic involvement of bone and 1,25 dihydroxy vitamin D(calcitriol) and parathyroid hormone- mediated hypercalcemia.³² A rapid rise of serum calcium (>13.5 mg/dL) causes delirium and coma. Chronic elevation may produce more subtle findings such as malaise, lethargy, mood disturbance, anorexia, and constipation, constitutional symptoms which may mistakenly be attributed to the patient's underlying disease. Hydration and

bisphosphonates are the main treatments. Denosumab, a monoclonal antibody that inhibits osteoclast function, is useful for bisphosphonate-refractory hypercalcemia.³³

Cachexia, Anorexia, and Malnutrition

Nutritional deficiencies and cachexia, which is mediated by chronic inflammation, have been associated with cognitive decline.^{34–37} The tumor, and its humoral response produce inflammatory cytokines, particularly IL-1, IL-6, and tumor necrosis factor alpha (TNF- α) which are associated with delirium and cognitive dysfunction by affecting serotonin and hypothalamic pathways.^{38–40}

Disorders due to deprivation of a single nutrient have been reported in cancer patients including the Wernicke Korsakoff syndrome (WKS) from thiamine deficiency, vitamin B12 deficiency, and niacin deficiency associated with carcinoid tumors; the latter two are uncommon. WKS is characterized by cognitive impairment, ocular signs, and ataxia and has traditionally been described with alcohol use, but is seen in the oncologic population.⁴¹ In a large retrospective review of WKS in cancer patients, the most common sign was cognitive impairment (100%) followed by ataxia (39%) and oculomotor signs (17%); MRI findings typical of WKS were found in only 30% of patients.⁴² Thiamine deficiency may result from malabsorption due to a structural lesion or secondary to diminished appetite, diarrhea, or vomiting. It may also result from hypermetabolism associated with illness from sepsis, fever, and steroid use. Rapidly growing tumors and hematologic malignancies can deplete thiamine stores due to rapid cellular turn over. Fluorouracil, a drug used to treat gastric and head and neck cancers, can produce thiamine deficiency.⁴³ Thiamine supplementation should be given to any cancer patient presenting with confusion.

PNS/AIS

Immune-mediated disorders, including classic paraneoplastic neurologic syndromes and more recently described autoimmune syndromes (AIS), can cause limbic encephalitis (LE) (Table 1).^{44–47} Unlike classic PNS, the AIS occur more commonly in younger patients, with or without a cancer diagnosis, and are responsive to treatment; the associated antibodies target extracellular surface antigens as opposed to intracellular neuronal antigens in PNS.

Antibodies most frequently associated with LE are Hu (small cell lung) and Ma (testicular) in PNS. LE is characterized by confusion, memory impairment, and psychiatric symptoms in association with CSF findings of pleocytosis, elevated IgG, or oligoclonal bands. MRI may show bilateral abnormalities in the medial temporal lobe on T2 weighted fluid-attenuated inversion recovery (FLAIR) imaging. Antibodies in the CSF are not necessary to establish the diagnosis, however, testing for these antibodies is important because their presence may indicate a specific tumor type as well as predict outcome. LE from AIS has a better response to immunotherapy and anti-tumor treatment and a better prognosis with a recovery of 80%.

Confusion: Indirect Relation to Cancer Treatment

Confusion attributed to cancer therapy should be a diagnosis of exclusion after considering cancer related causes, particularly metastatic disease. Many cancer treatments can cause

confusion (Table 3), and this review will focus upon those associated with acute encephalopathy, posterior reversible encephalopathy syndrome (PRES), and progressive multifocal leukoencephalopathy (PML) (Table 4).

Acute confusion may occur after the use of antineoplastic agents that cross the blood brain barrier (BBB) such as high dose cytarabine or methotrexate, procarbazine, 5-fluorouracil, and the nitrosoureas.^{48,49} Most episodes are idiosyncratic and reversible after drug withdrawal. However, ifosfamide encephalopathy can occur hours to days after administration and may be fatal; methylene blue may be helpful.⁵⁰ High dose methotrexate may produce a unique stroke-like syndrome of alternating focal deficits with encephalopathy, usually transient, and occurring several days after the second or third cycle.⁵¹ Other than an idiosyncratic reaction, confusion may be the result of an electrolyte disorder particularly with platins that cause hypomagnesemia, hypokalemia, and hypocalcemia, and the vinca alkaloids which may cause hyponatremia from SIADH.⁵² Seizure can manifest as encephalopathy resulting from either an electrolyte disturbance or from drug itself such as high dose busulphan.^{53,54} Partial complex seizures may present only as confusion and can be prolonged from non-convulsive status epilepticus which is detectable only by EEG. Seizures may also occur with intrathecal administration of any drug including methotrexate, cytarabine, thiopeta, steroids, or rituximab.

CNS complications occur in 10–65% of patients who undergo hematopoietic stem cell transplantation (HSCT) and are associated with poor outcome.^{55,56} Most neurologic complications occur within 100 days of transplant and manifest as seizure and encephalopathy. Seizures are most common immediately after the stem cell infusion and may be related to dimethyl sulfoxide used for cryopreservation. High dose busulphan and total body irradiation are other contributing factors during induction. Pancytopenia prior to bone marrow reconstitution and long term immunosuppression after allotransplantation predispose patients to delayed opportunistic CNS infections.

Small molecule inhibitors and novel T-cell therapies may cause confusion. Bortezomib, a proteasome inhibitor, has been associated with acute change in mental status.⁵⁷ Blinatumomab is a bispecific T-cell engaging antibody that is effective in acute lymphocytic leukemia.^{58,59} Somnolence, seizure, and encephalopathy occur in 15%–20% of treated patients. CNS symptoms typically resolve with discontinuation of the drug and have been attributed to acute release of inflammatory cytokines. A similar syndrome is seen after CAR T-cell therapy which is used to treat lymphoma or leukemia.^{60–63} It is often associated with confusion, psychiatric symptoms, seizure, and encephalopathy occurring within weeks of T-cell infusion. The etiology of the neurologic symptoms may be direct T-cell toxicity in the brain as CAR T-cells cross the BBB and are found in the CSF, or through systemic inflammatory mediators producing a cytokine release syndrome.⁶⁴ The cytokine release syndrome can range clinically from a mild flu-like syndrome with fever to multisystem organ failure and severe encephalopathy.

Ipilimumab, an immune check point inhibitor, is associated with encephalopathy.⁶⁵ Pathogenesis is thought to be due to elevated levels of proinflammatory cytokines. Ipilimumab and other check point inhibitors such as nivolumab and pembrolizumab may be

associated with an autoimmune thyroiditis which can present with confusion^{66–68}. In addition, autoimmune hypophysitis with confusion and diabetes insipidus is seen in 3% of patients treated with these agents. One case of ipilimumab-induced encephalopathy with a reversible splenic lesion in the corpus callosum has been reported.⁶⁹ The full spectrum of CNS toxicities from immune checkpoint inhibitors likely remains to be defined.

Posterior reversible encephalopathy syndrome (PRES) is a well-characterized clinico-radiographic entity of altered mental status and seizure in association with characteristic neuroimaging findings in the posterior white matter. In two large reviews of PRES in cancer patients, confusion occurred in 59%–71% of patients.^{70,71} PRES is associated with hypertension, the puerperium, and immunosuppressive agents used in organ and HSCT; more recently, it has been described with targeted agents, anti-angiogenic agents, and immune check point inhibitors.^{72–75}

In one review of 31 cancer patients, 55% had received chemotherapy or targeted agents in the month preceding PRES, with 35% receiving bevacizumab.⁷⁰ PRES typically resolves when the causative drug is withheld, but residual deficits from infarction or hemorrhage are more common in cancer patients.⁷⁶

PML, a fatal demyelinating disease caused by activation of the latent John Cunningham (JC) virus in an immunosuppressed patient, is a rare cause of confusion in cancer patients. PML is increasingly seen in those with hematologic cancers treated with monoclonal antibodies that target B and T cells such as rituximab, brentuximab, and alemtuzumab, and small molecules such as ruxolitinib.^{77–79} In addition, it is increasingly recognized as a complication of allogeneic HSCT due to chronic immunosuppression needed to prevent graft versus host disease.⁸⁰ Although brain biopsy is the gold standard for diagnosis, detection of JC virus in the CSF in association with typical white matter changes on neuroimaging is sufficient to confirm the diagnosis; however, the sensitivity of CSF PCR for JC virus is only 75% so in patients where PML is considered likely, a brain biopsy may still be necessary for diagnosis.^{77,81} Reconstitution of immune function is the only known treatment.

Conclusion

A rational clinical approach to the confused oncologic patient is one which identifies both direct and indirect related etiologies. Cancer itself affects the normal biologic milieu resulting in inflammatory, metabolic, and neurochemical changes not present in the general medical population. Such changes precipitate confusion from both resultant increased BBB permeability and systemic end organ dysfunction. With the rapid development of “mutation-based” clinical trials of targeted therapeutics and the growing armamentarium of biologic therapies, it is essential for the clinician to be familiar with the increasing association of delirium to newer agents.

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Key Points

1. Confusion is the most common neurologic symptom in cancer and may be directly related to cancer itself or to cancer treatment.
2. The under recognition of potentially reversible causes for delirium in the cancer patient results in prolonged hospital stays, distress for patient, family, and caregivers, and increased morbidity and mortality.
3. The current era of precision medicine is rapidly producing novel targeted and immune therapeutics that are associated with an emerging pattern of neurotoxicity that includes confusion as a common manifestation.

Table 1**Etiologies of Confusion: Cancer Related****Metabolic**

Electrolyte abnormality (hypomagnesemia, hypophosphatemia, hypo- hyponatremia)
 Tumor lysis syndrome
 Hypercalcemia of malignancy
 Cachexia/anorexia syndrome
 Thiamine deficiency
 Carcinoid syndrome/pellagra
 Endocrine dysfunction
 Adrenal-Addison/Cushing disease
 Thyroid-myxedema, thyrotoxicosis
 Parathyroid-hypo- and hyperparathyroidism

End organ failure

Liver-hepatic encephalopathy
 Kidney-uremic encephalopathy
 Brain-hypoxic encephalopathy
 Lung-carbon monoxide narcosis

Metastatic

Brain
 Leptomeningeal
 Gliomatosis/Lymphomatosis

Vascular

Embolic
 Nonbacterial thrombotic endocarditis
 Tumor (myxoma, lung, mucin secreting)
 Bone marrow
 Fat
 Infarction
 Disseminated intravascular coagulation (leukemia, breast, lung)
 Hypercoagulation
 Thrombocytosis (myeloproliferative disorders)
 Leukostasis (leukemia)
 Hyperviscosity (leukemia, multiple myeloma)
 Arterial and venous occlusion by direct tumor invasion
 Hemorrhage
 Hypocoagulation (myeloproliferative disorders)
 Brain metastases (melanoma, lung, germ cell, kidney)
 Thrombotic microangiopathy (gastric, breast, lung)
 Vasculitis (Hairy cell leukemia, Hodgkin disease)
 Intravascular lymphoma/Angiotropic lymphoma

Limbic encephalitis

	<u>Cancer</u>	<u>Associated antibody</u>
Paraneoplastic	Small cell lung	Anti-Hu
	Germ cell, testes	Anti-Ma
	Hodgkin lymphoma (Ophelia syndrome)	NMDAR, mGluR5, Hu
Autoimmune	Ovarian teratoma	NMDA
	Breast	AMPA
	Neuroendocrine lung	GABA b
	Thymus	LGI1
Inflammatory		
Cytokine release		
Interleukin 1, 6, and 8, interferon, tumor necrosis factor		

Abbreviations: NMDAR – N-methyl-D-aspartate receptor; mGluR5 – Metabotropic glutamate receptor 5; AMPA – Alpha-amino-3-hydroxy-5-methyl- isoxazolepropionic acid receptor; GABA b – gamma-aminobutyric acid; LGI1 – Leucine-rich, glioma inactivated 1

Table 2**Clinical Evaluation of the Confused Cancer Patient****Risk factors**

Advanced age
Advanced cancer
Pre-existing cognitive dysfunction
Pre-existing psychiatric disorder
Cardiovascular disease
Diabetes
Substance abuse

Neurologic examination

State of consciousness
Pupillary abnormalities, eye movements, funduscopy exam
Asterixis
Myoclonus
Muscle tone
Focal signs (hemiparesis, aphasia, ataxia)

Laboratory testingStructural

Brain MRI with gadolinium: metastases, hemorrhage, infarction, infection
Lumbar puncture: leptomeningeal disease, increased intracranial pressure, infection
EEG: nonconvulsive status epilepticus, triphasic waves

Blood

Complete blood count
Electrolytes (Na, K, Ca, Mg, Po4)
BUN and creatinine
Liver function and ammonia
Glucose
Thyroid function and cortisol
Lactate
Arterial blood gas
Thiamine, folic acid, Vitamin B12
Blood cultures
Autoimmune antibodies

Table 3**Confusion: Cancer Treatment Related**

I.	Cancer medications
a)	Supportive medications Antihistamines Amphetamines Anticholinergics Appetite stimulants (mitotane, aminoglutethimide) Benzodiazepines Corticosteroids H2 blockers Opioids
b)	Antineoplastic agents Standard chemotherapy agents Intrathecal chemotherapy Small –molecule inhibitors (PRES) Anti-angiogenic agents (stroke/PRES) Immune therapy (encephalopathy/PRES/PML) Targeted B and T cell agents CAR T –cell transfusion Immune check point inhibitors
II.	Hematopoietic stem cell transplantation Induction therapy (seizure /encephalopathy) Chronic immunosuppression (opportunistic infection, PML, PRES)
III.	Cranial radiation Radiation necrosis Delayed leukoencephalopathy
IV.	Surgery Pre-operative (old age, dementia, alcoholism, cardiac disease, diabetes) Intra-operative (hypoperfusion and anoxia, cerebral emboli) Post-operative (insomnia, medications, nutritional abnormality, infection, pulmonary embolus)

Abbreviations: PRES - posterior reversible encephalopathy syndrome; PML - progressive multifocal leukoencephalopathy

Table 4**Specific Cancer Therapeutics That Cause Confusion**

Encephalopathy	Seizure	PRES	PML
<u>Acute</u>	Busulfan	Bevacizumab	Alemtuzumab
Bortezomib	CAR T-cell therapy	Blinatumomab	Brentuximab
Blinatumomab	Carmustine	Bortezomib	Fludarabine
CAR T-cell therapy	Cisplatin	CAR T-cell therapy	Rituximab
Cisplatin	Cytarabine	Cisplatin	Rutolitinib
Etoposide	Etoposide	Carboplatin	
Fludarabine	Fludarabine	Docetaxel	
5-Fluorouracil	Ifosfamide	Ipilimumab	
Ifosfamide	L-Asparaginase	Irinotecan	
Interferon-alpha	Methotrexate	Oxaliplatin	
Interleukin-1	Vincristine	Paclitaxel	
Ipilimumab		Pazopanib	
L-Asparaginase		Rituximab	
Methotrexate		Sirolimus	
Nitrosoureas		Sorafenib	
Procarbazine		Sunitinib	
Tamoxifen		Tacrolimus	
Thiotepa		Vincristine	
Vincristine			
<u>Chronic</u>			
Carmustine			
Cytarabine			
Fludarabine			
Methotrexate			

Abbreviations: PRES – Posterior reversible encephalopathy syndrome; PML – Progressive multifocal encephalopathy