

Alexandrine Syndrome and Palliative Care: A Psychotic Reaction against Death: A Case Report

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Abstract

Background: Palliative care disclosure and death-facing can be traumatic for patients with advanced cancer. Some of them can suffer a psychotic breakdown that must be differentiated from a terminal delirium.

Objectives: To describe a psychiatric side effect from a palliative care announcement called the Alexandrine syndrome.

Methods: To illustrate this, we report the case of a patient with no past psychiatric history who, a few days after his palliative state has been announced, presented a major behavioral disorder with violence and paranoid delusions, heteroaggressivity against caregivers and autoaggressivity, that could not be explained by a somatic origin.

Results: With this case report, we would like to point out the importance of an unreported palliative clinical situation which cannot be explained by an organic substratum.

An intense fear of death expressed by the patient with an outburst of defense mechanisms can lead to a brief psychiatric decompensation without any preexisting state of psychosis.

Conclusion: The hypothesis of an Alexandrine syndrome should be considered in palliative care in advanced cancer patients experiencing massive anxiety when facing death. This infrequent diagnosis should especially be hypothesized when a patient presents a feature with sudden or recent profound mental disorder following an oncologist consultation with palliative state disclosure. Physical and psychological consequences must not be neglected for patients, as well as disturbing occurrences for the medical team involved. Therefore, oncologists and palliative doctors should be aware of this possibility. Collaboration between psychiatrists and palliative and oncologic teams is recommended to better manage this psychiatric situation.

Keywords: Acute psychotic episode; Palliative care; Alexandrine syndrome; Death anxiety; Advanced cancer

Introduction

Patients with advanced cancer can be confronted with an interaction between their physical impairment and their psychic reality regarding a possible impending death. Palliative status disclosure can generate major stress with the reality of death and the occurrence of an atypical acute psychotic symptomatology [1].

This special feature in palliative care was first identified and named Alexandrine syndrome by Dr. Gomas in 2005 [2]. We hypothesize that this infrequent psychotic breakdown must not be related to the organic deterioration of the illness or to the decompensation of a preexisting psychosis state and systematically assimilated to a terminal delirium. It should be related to overwhelmed defense mechanisms.

We will illustrate this by reporting the case of a patient being diagnosed at a palliative stage who developed an Alexandrine syndrome. Differential diagnosis and management will be discussed.

Case Report

A 59-year-old man has been followed for 5 months for adenocarcinoma at the gastroesophageal junction with lung metastasis. One week after the implementation of chemotherapy with FOLFOX regimen, he is hospitalized in a general hospital for pneumonia and delirium. Brain CT scan do not show any metastasis. Within two days, infection and mental state improve with respectively tazocilline and gentamicine and haloperidol prescriptions (2,5 mg IV). Patient is transferred to the oncologic department for follow-up. At this point, psychiatric evaluation does not reveal any recurrence of delirium or posttraumatic stress disorder caused by the experience of being delirious. The patient has no past psychiatric history and, in particular, is not known to have psychotic disorders.

Four days later, the psychiatrist is called in early morning to make a new evaluation, regarding a sudden change of his behavior. He has become suspicious, refusing to shake hands with doctors or answering the telephone during the consultation, presenting a state of mutism and either refusing to answer questions or only giving laconic answers. Paranoid delusions are present so the health care team is "nasty" with him and wants to harm him. Risperidone 1 mg bid is prescribed. Late afternoon, the patient becomes more and more agitated and receives one injection of zuclopenthixol acetate 50 mg repeated 2 hours later plus 5 mg of midazolam and has to be constrained. He is calm and rests for a short period of time, but around 10 pm, starts struggling to get out of bed, succeeds in getting rid of his bonds and becomes more and more violent, aggressive, breaks his urinal glass and threatens with a shard any healthcare member who dares to approach him or threatens to harm himself by slitting his own throat. He gets into the bathroom, attempts to lock the door and tries to jump out the window.

Finally, the police are called and after an hour long negotiation, one of the eight officers succeeds in calming down the patient who accepts to be transferred to the emergency room at the general hospital. All the somatic investigations (neurologic with brain magnetic resonance imaging, EEG monitoring and lumbar puncture; cardiac with doppler echocardiography and transthoracic echocardiography, X-ray of thorax and abdomen) are inconclusive.

No supra aortic stenosis or cardiopathies with embolism are found. A paraneoplastic limbic encephalitis and carcinomatous meningitidis are also ruled out. No seizure with epilepsy can be found. No metabolic disorders are found. The psychiatrist from the liaison psychiatric department does not find any suicidal ideations or delirium. Brief psychotic episode with persecution ideas is diagnosed whilst patient has recovered and was discharged.

3 weeks later, the patient is referred for dysphagia investigation to the oncologic department. A new consultation is carried out with the psychiatrist to ensure that the patient is no longer dangerous to himself and to others. Patient is seen with his daughter.

He has been unemployed for one year (used to be a day worker in construction). His first wife died 19 years ago at home from a generalized lung cancer and the patient was deeply involved as a caregiver: delivering nursing care and medications including opiates by PCA. "She died in my arms".

After cancer disclosure and the realization that he would not be cured, the patient remembers being suspicious, having the feeling that the neighbors were staring at him strangely and that he was losing his second wife. His daughter points out the fact that her father's professional and personal life is in turmoil with consequences both financial and personal (unemployment and marital conflict).

Then, after the first administration of chemotherapy (infusion of FOLFOX), the patient starts to develop visual illusions and assimilates the infusion of Folfox to the PCA of opiates that his first wife was administered late in her life. He is convinced he is at a terminal stage. Moreover, while he is hospitalized to treat his pneumonia, the nurses want to take off the Folfox infusion and the patient assimilates that to his own end of life as it was so for his wife when she died and the PCA was taken off.

Discussion

Patients with an advanced cancer must struggle with many stress factors related to the evolution of the disease: fear of suffering death,

loss of autonomy, impaired body image and dependency. The level of psychological distress will depend on personality features, coping styles, optimism, social support and will impact the patient's quality of life [3]. It might be the harbinger of psychiatric disorders such as anxiety, depression or delirium [4,5]. Surprisingly, few studies report the incidence of brief psychotic episodes in palliative care while patients receiving terminal care experience various kinds of psychological burden [6].

Sirois reported the case of a 60-year-old patient followed for lung cancer who developed a psychotic breakdown after his hospitalization for hemoptysis [1].

Onishi et al. reported the case of a 49-year-old woman with advanced uterine carcinoma who, during her hospitalization, developed a brief psychotic episode after witnessing the death of others patients from gynecological cancers [7]. The same authors described another case of a 77-year-old patient with advanced gastric carcinoma who presented a brief psychotic episode following an epistaxis that the patient will attribute in his fantasy to terminal life [6].

In 2005, Dr. Gomas reported the case of a 67-year-old woman treated for an oesophageal cancer and who developed a few hours after her oncologist had delivered a gloomy prognosis to her, a massive outburst with violence, screams, paranoid delusions and death talking.

The medical team was unable to calm her down. Huge amounts of antipsychotics in intramuscular (300 mg of loxapine, 800 mg of tiapride per day) and subcutaneous administration of 100 mg of midazolam hardly sedated her. For 19 days, the patient was alternating phases of aggressivity and coma. She spontaneously recovered and told the medical team: "do not ever talk to me again about my death". She peacefully died 1, 5 months later without presenting any psychotic breakdown anymore.

Confronted to such an unusual clinical case, the medical team asked the patient for the permission to publish her case. As a Russian translator, she wanted to call her syndrome by the beloved given name she had always wanted to have: Alexandrine as the "Tsarina"! [2].

Differential diagnosis

These are summarized in Table 1. We would like to emphasize the specific diagnosis of delirium. Delirium in palliative care and especially in terminally ill is a common diagnosis with multiple causes: toxic, infection, metabolic, neurologic, and traumatic [8-10]. Nevertheless, in palliative situation, in more than 50% of delirium, none of the potential causes will be found [11].

Delirium has to be differentiated from a brief psychotic episode where we would have no alteration of consciousness and systematized delusions and congruence between behavior and delirious thematic. What could be diagnosed as a terminal delirium is to be considered more as an acute brief psychotic episode related to a severe death anxiety that has been reactivated either by the hospitalization in palliative care or by short lethal prognosis disclosure. In this hypothesis, defense mechanisms are no longer efficient and the patient being overwhelmed by his anguish expresses his fears in a psychotic way called Alexandrine syndrome.

	Alexandrine Syndrome	Delirium	Acute Anxiety Episode	Preexisting Psychotic Episode	Psychotic Disorder due to a General Medical Condition	Substance-Induced Psychotic Disorder	Major Depressive Disorder with Psychotic Features	Agitated catatonia due to a general medical condition
Prevalence	2% (2)	42-88% (10)	10% (22)	0.5-1.5% (23)	0.21-0.54% (21)	7-25% (21)	14.3% (22)	21 % (24)
Medications : Corticosteroid, opioids	-	++	+	-	-	+++	-	+
Mood disorders	-	+	+	-	-	-	+++	+++
Pleomorphism of symptomatology	-	++		-	+++	+	-	+
Guilt/punishment wishing	-	-	-	-	-	-	++	+/-
Persecution delusions	++	+++	-	++	++	+	-	-
Hostile reaction	+++	++	-	++	++	++	+	++
Disorientation	-	++	-	-	-	-	-	-
Disturbance of consciousness	-	++	-	-	-	-	-	-
Tolerance to high doses of antipsychotics	+++	-	-	+	+	+	-	+
Disturbance is caused by direct physiological consequences of a general medical condition	-	+++	+	-	+++	-	-	+/-
History of past psychiatric disorders	-	+/-	+/-	+++	-	-	-	++

Table 1: Differential diagnosis of Alexandrine syndrome.

Clinical features of the Alexandrine syndrome

The main features are [2]:

- Prodromic symptoms such as emotional exacerbation, intense anxiety
- Acute agitation that occurs suddenly, heteroaggressivity, delirious ideations with a persecution thematic against healthcare team, and sometimes, but not always, hallucinations,
- Without any metabolic, pharmacological (e.g.opiates),visceral or metastatic (e.g. brain) explanation,
- Direct and sudden link with a confrontation to death anxiety but not in a terminal state,
- Strong wish to “struggle for life”,
- Duration over 48 hours,
- Intensity of the physical outburst and violence,
- Resistance to common and usual doses of sedatives,
- Reversibility of all symptoms with the possibility to communicate again with the medical team in a peaceful manner.

Predisposing factors of Alexandrine syndrome

Usually, patients who might develop such a syndrome will have:

- Rigidity of their psychic thoughts with a tendency to master and self-control everything in their life,
- Some difficulties to communicate with their relatives about illness,
- Existence of a gap between the course of the disease and its perception,
- Brutal disclosure of a therapeutic deadlock and short prognosis.

Specificity of the management of an Alexandrine syndrome

Alexandrine syndrome has to be considered a medical and psychiatric emergency. Regarding the explosive features of the behavior presented by these patients, a strong sedation is recommended to alleviate the psychological suffering. Sedation for refractory psychological and existential distress or suffering remains controversial and debated [12,13] with ethical issues [14]. First, differential diagnosis must be assessed and then all pharmacological prescriptions must be individualized and adapted within a titration process and the lowest efficiency posology with the fewer side effects. In order to decrease the agitated and restlessness symptomatology and alleviate the patient’s distress, psychotropic doses have been substantially higher than the usual recommended doses. During the

agitated phase, the intra muscular administration will be privileged but all the non-pharmacological approaches will also be considered [15]. These patients' capacity to resist to high doses of neuroleptics considering their impaired medical condition and sometimes old age could be an indirect sign of underlying psychosis rather than a simple delirium [1]. Identification and respect of the patient's defense mechanisms is paramount. Nutrition and hydration must be continued if possible.

Regarding the therapeutic classes of drugs used, first choice will be neuroleptics to treat agitation near the end of life [16]. Mainly, haloperidol, chlorpromazine, olanzapine are used but frequently a neuroleptic rotation must be done regarding a lack of treatment efficacy of first line choice [17,18].

Theoretical explanations of Alexandrine syndrome

As Alexandrine syndrome usually occurs in palliative care and in terminal life, it could be assimilated to an equivalent of an end of life "Amok". Amok comes from the Malaysian word "Amuk" which means uncontrollable rage. Amok was first described in East Asia among runners, with the use of the expression "Run Amok", for those runners who are suddenly taken into a frenetic and murderous run involving lots of frustration and generating a desire of revenge with auto and heteroaggressivity [19]. Alexandrine syndrome with this uncontrollable rage, could be the western illustration of Amok and considered as a culture-specific explosive behavioral disorder in DSM-IV [20].

Alexandrine syndrome can also be explained from a psychoanalytic point of view. It would express all the patient's ambivalence between demand and desire. The frenetic agitation of the patient and the outbursts of violence can be explained by an unconscious desire of life when faced with impending death. This struggle for life at any price can also be understood as a desire for death in order to no longer be confronted to torments of uncertainty while waiting for death to come.

Patients try to protect themselves against the psychic trauma generated by prognosis or palliative state announcements that will create a sense of collapsing that threatens the sense of continuity and existence of each subject. Confronted with the discovery of impending death, the subject wants to restore the urge to live.

From the psychiatric nosography of DSM-5, Alexandrine syndrome would be considered as a brief psychotic disorder [21,22]. However, this international classification for mental disorders has not been developed to take into account palliative and end of life specificities. Actually, DSM-5 no longer considers as a traumatic event a mortal disease or a threat to physical integrity which an advanced cancer is [23,24]. Yet, Alexandrine syndrome is really a psychotraumatic phenomenon. Confrontation with the potential reality of death represents a real aggression for the patient who will need a reorganization of his psychic system in order to "survive" this traumatic event.

Conclusion

Palliative patients can present a brief psychotic episode with outbursts of violence called Alexandrine syndrome. The intensity of physical violence associated with paranoid delusions against the healthcare team and resistance to usual sedation are typical features of this syndrome. It can be the result of a complex interaction between physical, physiological and psychological factors. Nevertheless, the

medical team must always rule out potential somatic causes and differential diagnosis before considering such a hypothesis. Alexandrine syndrome occurrence can be understood as a struggle for life against the unbearable threat of a deadly sentence. In a preventive way, healthcare professionals working in the palliative field should always be cautious before approaching death with their patients.

Collaboration between psychiatrist and palliative medical teams is recommended either for prevention or psychiatric management.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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