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Drug-Induced Agranulocytosis in Elderly Patients: Diagnosis and Management of Life-Threatening Infections and Septic Shock

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Abstract

In this paper, we discuss the diagnosis and management of life-threatening infections including septic shock, in elderly patients presenting with acute drug-induced neutropenia (neutrophil count of <0.5 x 10^9/L). Also known as "idiopathic agranulocytosis," it remains a potentially serious adverse effect of various drugs, especially in vulnerable elderly patients. Clinical manifestations include severe deep tissue infections (e.g. pneumonia), septicemia and septic shock in approximately two-thirds of cases. Recently, several factors have been identified in order to help recognize patients with a poor prognosis. These include: Old age (>65 years), septicemia or septic shock, metabolic disorders such as renal failure and a neutrophil count below 0.1 × 10^9/L. In this potentially life-threatening disorder, modern management with broad-spectrum antibiotics and hematopoietic growth factors (particularly G-CSF), is likely to improve the prognosis, even in elderly patients.

Keywords: Agranulocytosis; Neutropenia; Idiosyncratic drug-induced agranulocytosis; Infections; Elderly; Antibiotics; Hematopoietic growth factor

Introduction

Agranulocytosis or acute neutropenia is characterized by a profound decrease or an absolute lack of circulating granulocytes, classically resulting in a neutrophil count of <0.5 x 10^9/L [1,2]. The term "agranulocytosis" was first introduced in 1922 by Schultz for cases of acute and severe pharyngeal infections, associated with a lack of granulocytes in the blood. In the majority of patients, the neutrophil count is under 0.1 x 10^9/L.

Patients with severe acute neutropenia are at high risk of developing complications such as pyrexia, which in some cases may be a sign of severe or life-threatening infections [2,3]. This is particularly frequent in compromised, vulnerable elderly patients and may result in a fatal outcome.

In this paper, we report and discuss the diagnosis and management of life-threatening infections and septic shock in elderly patients presenting with acute severe neutropenia.

Criteria for the definition of idiopathic drug-induced agranulocytosis

Most, but not all cases of agranulocytosis occur as a result of exposure to drugs. Two examples include chemotherapy (chemotherapy induced-agranulocytosis) and immune modulator agents or biotherapies. The latter results in "idiosyncratic drug-induced agranulocytosis", (as we have previously reported [4]). Either the drug itself or one of its metabolites may be the causative agent [5]. Currently, the recommended criteria for diagnosing blood cytopenias and for implicating a drug as a causative agent in neutropenia have been derived from an international consensus meeting [2,6]. These criteria are outlined in Table 1.

Definition of agranulocytosis	Criteria of drug imputability
Neutrophil count <0.5 x 109/L ± existence of a fever and/or any signs of infection	Onset of agranulocytosis during treatment or within 7 days of exposure to the drug, with a complete recovery in neutrophil count of more than 1.5 x 109/L within one month of discontinuing the drug
	Recurrence of agranulocytosis upon re-exposure to the drug (this is rarely observed, as the high risk of mortality contra-indicates redaministration of the drug)
	Exclusion criteria: history of congenital neutropenia or immune mediated neutropenia, recent infectious disease (particularly recent viral infection), recent chemotherapy and/or radiotherapy and/or immunotherapy* and existence of an underlying hematological disease

*: Immunoglobulins, interferon, anti-TNF antibodies, anti-CD20 (rituximab)

Table 1: Criteria for idiosyncratic drug-induced agranulocytosis [2,3,6].

This is of particular importance in elderly patients, because in this population there are many causes of neutropenia. Thus strict criteria are needed in order to definite drug-induced agranulocytosis. In practice, it remains a diagnosis of exclusion. In fact to affirm the diagnosis, re-introduction of the causative drug is avoided.

Epidemiology of idiopathic agranulocytosis

Idiosyncratic drug-induced agranulocytosis is a rare disorder. In Europe, the annual incidence is between 1.6 and 9.2 cases per million population [3,7-10]. In the USA, reported rates range from 2.4 to 15.4 per million per year [11]. In our experience (an observational study in a French hospital between 1996 and 2003), the annual incidence of symptomatic idiosyncratic drug-induced agranulocytosis remained stable, with approximately 6 cases per million population [12]. Differences in the incidence may be due to different methods/ inclusion criteria used in published studies [3,6]. It is important to keep in mind that the incidence remains unchanged, despite various preventative measures including the withdrawal from use of several incriminated drugs (which carry a high risk of idiosyncratic drug induced neutropenia), and increased levels of medical awareness and pharmacovigilance [6].

The incidence of drug-induced agranulocytosis increases with age. More than half of cases occur in people over 60 years of age, probably reflecting the increased use of prescribed medication in older age groups [2-5]. In our cohort study (n=91), 67% of patients were aged 65 years or over [12]. Again, this is likely due to the fact that the elderly are exposed to many more drugs than younger people. According to the literature, a high proportion of elderly patients take four to five medications on a regular basis. In a small study (including patients with cardiac failure, diabetes mellitus, renal failure, cancer) performed in our Department, we found that elderly patients frequently take more than ten different classes of medication (personal communications). In this population, we also observed a relationship between the patient categories: "good health", "frailty", "too sick" and the number of different drug classes prescribed.

In practice, poly-medication represents a significant challenge to the physician when determining the responsible drug. Self-administration of drugs unknown to the medical team (for example, without prescription in the drug chart or that have not been mentioned in the past medical history) cause further difficulties especially in confused and disorientated elderly patients.

Drugs implicated in idiopathic agranulocytosis

Firstly, it is important to note that almost all classes of drugs have been implicated in this acute adverse event [2,3,12-16], but for the majority the risk appears to be very small [3]. However, for drugs such as antithyroid medications, ticlopidine, clozapine, sulfasalazine, trimethoprim-sulfametoxazole (cotrimoxazole) and dipyrone, the risk may be higher [3,17,18]. For example, for antithyroid drugs, a risk of 3 per 10,000 users has been reported [2]. For ticlopidine, the risk is more than 100-fold higher [9]. Clozapine induces agranulocytosis in almost 1% of patients, particularly in the first three months of treatment, with older patients and females being at higher risk [18].

In our single center cohort [12], the most frequent causative agents were: antibiotics (25%), particularly β-lactams and cotrimoxazole, which has strong implications on the management of the episode (cross-reactivity of antibiotic molecules); antithyroid drugs such as neomercazole (23%); antiplatelet agents such as ticlopidine (16%); neuroleptic and antiepileptic agents (11%); and non-steroidal anti-inflammatory drugs (8%). In this cohort, patients taking immunosuppressive drugs such as steroids, methotrexate, cyclophosphamid, cyclosporine, mycophenolate mofetil or azathioprim and bio-therapeutic agents as interferon, rituximab, infliximab or bortezomid were excluded.

These findings are similar to two recent reports that incriminated the same drug families [17,19]. In our cohort study, two thirds of patients received more than two drugs (mean of three), which accounts for the difficulty in identifying the drug responsible for the agranulocytosis. In this cohort, no over the-counter medications ("self medication") were identified as causative agents [11]. No inappropriate prescriptions, including the use of drugs that pose more risks than benefits or errors in dose or duration of treatment were identified. Nevertheless, in elderly patients over 80 years old, we observed that these patients frequently take a mean of eight drugs (1 to 17).

Clinical manifestations of drug-induced neutropenia and agranulocytosis

Initially, elderly patients with drug-induced acute neutropenia or agranulocytosis usually presents with fever, which is often the earliest and sometimes the only sign, associated with general malaise including rigors [2,3,14,20]. They also commonly present with a non-specific sore throat. More rarely, especially in compromised elderly patients, presentation is with a sudden, severe and potentially life-threatening infection [3].

It is important to note that without medical intervention, in particular immediate antibiotic administration, most elderly patients (>60% in our experience) develop severe and potentially life-threatening infections with signs of general sepsis and septicemia (fever, rigor, hypotension), while some have clinical signs of pneumonia as well as anorectal, skin or oropharyngeal infections and septic shock [2,3,13,14,20]. In such elderly patients, clinical manifestations were generally more severe, with septicemia or septic shock in at least two-thirds of cases, as previously published in [21-23].

In this setting, we also observed deterioration in several co morbidities such as cardiac failure, renal failure, diabetes mellitus or rheumatoid arthritis which may be difficult to manage or become life-threatening. Clinicians must keep in mind that signs of these infections are often atypical as a result of the neutropenia, e.g. no purulent sputum, no X-ray changes in pneumonia [2]. It should be noted that when antibiotics are administered prophylactically, or at the beginning of the event, both the patient's complaints and the physical findings may be "masked." Fever is often the only clinical sign detected [2,11].

As in patients receiving chemotherapy for the treatment of cancer, the occurrence and type of infections (bacterial or fungal) depends on the degree and duration of the neutropenia [2,21]. In our experience [12], a causative pathogen, typically Gram-negative bacilli or Gram-positive cocci (mainly *Staphylococcus spp.*), was isolated in 30% of cases in one series [2]. Fungi are also involved as secondary infective agents (>10%). In some rare instances, which are often poorly defined, patients remained asymptomatic [2,3,24]. This supports the case for routine monitoring of blood counts in individuals receiving high-risk medications such as antithyroid drugs, as recommended by Tajiri et al. [24,25], or ticlopidine [3] in order to detect this side effect and avoid complications early on.

Differential diagnosis of acute neutropenia

Theoretically, acute neutropenia as with agranulocytosis is classically diagnosed by a blood sample, with a neutrophil count of <0.5 x 10^9/L, [1,2]. In the majority of patients, the neutrophil count is under 0.1 x 10^9/L. In practice and in the literature, such severe neutropenia has been shown to be attributable to drugs in 70 to 90% of cases [2-4].

In the Berlin prospective Case-Control Surveillance Study of Serious Rare Blood Dyscrasias, acute agranulocytosis was found to be drug-related in 97% of cases as reported by Andersohn et al. [4]. Thus in practice, drug-induced neutropenia or agranulocytosis should be always be considered, even in cases where another cause seems likely. In this context, the clinician must keep in mind that in all cases, the patient's medication history must be carefully obtained in chronological order so that the suspected agent(s) may be identified [2].

The differential diagnosis of agranulocytosis in elderly patients includes a limited number of conditions [2]. In clinical practice, the main differential diagnose includes myelodysplastic syndromes [2,12]. Thus, in our opinion, bone marrow examination may be required in all patients in order to exclude an underlying pathology [25]. In patients with drug-induced agranulocytosis, the bone marrow typically shows a lack of mature myeloid cells, whereas in other cases, immature cells from the myelocyte stage are preserved. Acute agranulocytosis is the result of bone marrow damage which leads to a stop in the production of granulocytes.

Others situations include: neutropenia secondary to sepsis, particularly viral infections or bacterial infections (severe Gram negative infections with *Salmonella sp.*, *Klebsiella sp.*), tuberculosis, *Brucella sp.*); neutropenia associated with hypersplenism (e.g. alcoholic cirrhosis); and/or vitamins B9 and B12 deficiencies. Prognosis and mortality rate of drug-induced agranulocytosis in compromised patients Over the past twenty years, the mortality rate for idiosyncratic drug-induced agranulocytosis or severe neutropenia was 10-16% in European studies [2,13,21]. However, this has recently fallen to 5% (range, 2.5 to 10%) in several studies which included a majority of younger patients (treated for thyroid disorders with neomercazole).

This is likely due to improved recognition, management and treatment of the condition as demonstrated by Andersohn et al. and by ourselves [2,3,12]. In elderly patients, the prognosis is probably more severe. In our experience (more than 200 cases studied), all deaths were observed in the elderly, especially in severely compromised patients (due to severe sepsis or acute deterioration of co morbidities).

The highest mortality rate is observed in frail patients: older patients (>65 years), as well as those with renal failure (defined as serum creatinine level >120 μmol/L), bacteraemia or shock at diagnosis or low neutrophil count, as first reported by Julia et al. [2,21] and confirmed by our team [20,22,26].

We also found that a neutrophil count of <0.1 x 109/L at diagnosis, as well as septicemia and/or shock, were variables that were significantly associated with a longer neutrophil recovery time, and indirectly as a prognostic factor. In our cohort, bone marrow showing a lack of myeloid cells was not found to be associated with a delayed recovery time (using uni- and multivariate analysis) [26].

In contrast, the use of hematopoietic growth factors was associated with a shorter neutrophil recovery time (see the next section). In a recent systematic review by Andersohn et al. [3], which included 492 published case reports of agranulocytosis, it was shown that patients with a neutrophil count of <0.1 x 109/L had a higher rate of localized infections (59% versus 39%, p<0.001), sepsis (20% versus 6%, p<0.001) and fatal complications (10% versus 3%, p<0.001) than those with a neutrophil nadir ≥0.1 x 10^9/L.

Management of drug-induced agranulocytosis in elderly patients prevention

In our opinion, routine monitoring in patients taking medications with a confirmed, albeit rare association with neutropenia or agranulocytosis, is not worthwhile [2]. However, routine monitoring for agranulocytosis is required in some high-risk drugs, such as clozapine, ticlopidine and antithyroid drugs [2,6,24,25].

General measures

The management of idiosyncratic drug-induced neutropenia begins with the immediate withdrawal of any medications, which may potentially be responsible [2,12,13]. The patient's medication history must be carefully obtained in chronological order so that the suspected agent(s) may be identified. Auto-administration of drugs must exclude ('police interrogation').

Importantly, the appropriate pharmacovigilence center must be notified of all cases of drug-induced neutropenia or agranulocytosis [3]. Patients at high risk of infection in regards to the prognosis of drug-induced neutropenia [see the section below]) should be admitted to hospital without delay [3,27]. Patient isolation and the use of prophylactic antibiotics (e.g. for the gastrointestinal tract) have been proposed, but their usefulness in limiting the risk of infection has not been documented or clinically proven [2].

It should be noted that as a result of neutrophil deficiency, both the patient's symptoms and the physical findings may be altered, and fever may be the only clinical sign (see the section clinical manifestations) [26]. Preventive measures include good hygiene and infection control, paying particular attention to high-risk areas such as the mouth, skin and perineum [2,12].

In case of fever or signs of sepsis, multiple bacterial samples should be collected in all suspected sites of infection, (blood, urine and stool cultures) [2,3,27]. After one week of fever, deep and invasive mycosis (candidosis, aspergillosis, mucormycosis) should also be screened for systematically. Concomitant measures include aggressive treatment of confirmed or potential sepsis, as well as the prevention of secondary infections [2,20].

The majority of elderly patients with agranulocytosis are frail with multiple co morbidities, which pose additional challenges in terms of clinical management. Together, these factors contribute towards the poor outcome observed in such cases.

Multiple comorbidities in vulnerable patients often limit the use and tolerance of conventional therapies. Aggressive volume resuscitation in a frail patient with sepsis or renal impairment is more likely to lead to acute heart failure and electrolyte imbalances. Similarly, vasodilators are more likely to lead to progressive renal failure.

Antibiotic therapy

The occurrence of sepsis in drug-induced agranulocytosis requires prompt management, including the administration of broad-spectrum intravenous antibiotics (after blood, urine and any other relevant samples have been taken for culture) [2,12,13,20]).

Empiric, broad-spectrum antibacterial therapy is generally the best treatment, but the choice of antibiotic used may need to be adapted depending on the nature of the sepsis, the clinical status of the patient, local patterns of antibiotic resistance and previous antibiotic use [2,20].

In our department, first line therapy usually includes a combination of cephalosporins, quinolones or aminoglycosides [12,22]. Of course, ureidopenicillins beta-lactam/beta-lactamase inhibitor combinations, such as carbapenems or imipenem can also be safely used in cases of antibiotic resistance [2,3,27]. The addition of intravenous vancomycin or teicoplanin is considered in patients at high risk of serious gram-positive infections or after 48 hours of continued fever despite first line antibiotic therapy (consisting of at least a cephalosporin) [2,3,27].

In patients with a persistent fever despite the use of broad-spectrum antibiotics (active against Gram-negative bacilli or Gram-positive cocci), or routinely after 1 week of fever, the addition of empirical antifungal agents should be considered, such as amphotericin B or related derivates (e.g. liposomal preparation of amphotericin) and voriconazol or caspofungin [20,27].

When an antibiotic is suspected of being the causative agent resulting in neutropenia, one should keep in mind the potential for antibody cross-reactivity, and therefore the choice of further antibiotics to be used should be carefully considered [2,3].

Indications for hematopoietic growth factors

Since 1985, two-thirds of reported cases of drug-induced agranulocytosis have been treated with hematopoietic growth factors, such as Granulocyte and Granulocyte-Macrophage-Colony Stimulating factor (G-CSF and GM-CSF) [3,28-32]. The most recent, major studies on hematopoietic growth factor use in drug-induced agranulocytosis are described in Table 2 [3,22,29-32].

Type of study and target population	Main results
Systematic review of all published cases (n=492); All patients with idiosyncratic drug-induced agranulocytosis [3]	Treatment with hematopoietic growth factors was associated with a statistically significantly lower rate of infectious and fatal complications, in cases with a neutrophil count <0.1 x 10^9/L
Meta-analysis (n=118); All patients with idiosyncratic drug-induced agranulocytosis [30]	G-CSF or GM-CSF (100 to 600 µg/day) reduced the mean time to neutrophil recovery (neutrophil count >0.5 x 109/L) from 10 to 7.7 days, in cases with a neutrophil count <0.1 x 10^9/L, and reduced the mortality rate from 16 to 4.2%
Case control study, retrospective analysis (n=70); All patients with idiosyncratic drug-induced agranulocytosis [29]	G-CSF and GM-CSF (100 to 600 mg/day) reduced the recovery of neutrophil count from 7 to 4 days, particularly in patients with a neutrophil count <0.1 x 10^9/L
Cohort study, retrospective analysis (n=54); Patients with idiosyncratic drug-induced agranulocytosis >65 years of age, with poor prognostic factors [22]	G-CSF (300 mg/day) significantly reduced the mean duration for hematological recovery from 8.8 to 6.6 days (p <0.04). G-CSF reduced the global cost
Cohort study, retrospective analysis (n = 20); Patients with antithyroid drug-induced agranulocytosis and poor prognostic factors [28]	G-CSF (300 µg/day) significantly reduced the mean durations of hematological recovery, antibiotic therapy and hospitalization from: 11.6 to 6.8 days, 12 to 7.5 days and 13 to 7.3 days, respectively (p <0.05 in all cases). G-CSF reduced the global cost
Cohort study, retrospective analysis (n = 145); All patients with idiosyncratic drug-induced agranulocytosis [31]	G-CSF shortens time to recovery in patients with agranulocytosis
Prospective randomized study (n = 24); All patients with antithyroid drug-induced agranulocytosis [32]	G-CSF (100 to 200 mg/day) did not significantly reduce the mean duration for hematological recovery
G-CSF: Granulocyte-Colony Stimulating factor. GM-CSF: Granulocyte-Macrophage-Colony Stimulating factor.	

Table 2: Recent studies on the use of hematopoietic growth factorss in idiosyncratic drug-induced agranulocytosis (adapted from [2,6,20]).

In fact in the majority of these studies, G-CSF and GM-CSF (at a mean dose of 300 µg/day) were found to be useful in shortening the duration of blood count recovery time, without inducing any major toxic or adverse effects, particularly in patients with poor prognostic factors (i.e. particularly vulnerable patients as described below) [22,26,28,33,34].

The recent systematic review of all published case reports of non-chemotherapy drug-induced agranulocytosis by Andersohn et al. [3] confirms this data. A recent study by Ibanez et al. (Barcelona cohort) also concludes that G-CSF shortens recovery time in patients with agranulocytosis [31]. However, it is important to note that only one study reported a lower mortality rate with this therapy [30].

From an evidence based medicine perspective, it should be kept in mind that the only prospective randomized study available did not confirm any benefit of G-CSF [32]. A total of 24 patients with antithyroid-related drug-induced agranulocytosis were included in the

study. It is likely that both the small size of the cohort as well as the administration of an inappropriately low dose of G-CSF (100 to 200 µg/day) contributed towards these negative results.

Conclusion

To date, idiosyncratic drug-induced agranulocytosis or acute severe neutropenia remains a potentially serious adverse event, particularly in elderly patients due to the frequency of associated complications such as severe sepsis with deep tissue infections (e.g., pneumonia), life threatening infections, septicemia and septic shock (in two-thirds of patients).

Nevertheless, in this potentially life-threatening disorder, modern management with broad-spectrum antibiotics and use of hematopoietic growth factors such as G-CSF in cases of severe agranulocytosis (neutrophil count of $<0.1 \times 10^9$/L), is likely to improve the prognosis.

Conflict of interest

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