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ORIGINAL RESEARCH ARTICLE

Idiosyncratic Drug-Induced Severe Neutropenia and Agranulocytosis in Elderly Patients (≥75 years): A Monocentric Cohort Study of 61 Cases

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Abstract

Background Little data is currently available in the literature on neutropenia and agranulocytosis in the elderly, and, to our knowledge, idiosyncratic drug-induced agranulocytosis is particularly poorly covered, or not at all.

Objective We herein describe the clinical picture and outcome of patients aged ≥75 years with established idiosyncratic drug-induced agranulocytosis.

Patients and Methods Data from 61 patients over 75 years old with idiosyncratic drug-induced agranulocytosis were retrospectively reviewed. All cases were extracted from a cohort study on agranulocytosis ($n = 203$) in the Strasbourg University Hospitals (Strasbourg, France), a referral center.

Results The mean age was 84.9 years (range 75–95), the gender ratio (F/M) was 2.4. Underlying diseases were present in 74 %. The most frequent causative drugs were antibiotics (43.8 %), antithyroid drugs (15.8 %), neuroleptic and anti-epileptic agents (12.3 %), and antiaggregant platelet agents (10.5 %). The primary clinical features during hospitalization included isolated fever (27.6 %), septicemia or septic shock (24.1 %), and pneumonia (20.7 %). The mean neutrophil count at nadir was 0.15×10^9/L (range 0–0.4). All febrile patients were treated with broad-spectrum antibiotics and 36 with hematopoietic growth factors. Outcome was favorable in 85.3 % of patients; nine patients died. Two elderly patients (3.3 %) died of uncontrolled septic shock relating to the depth of the neutropenia. Comparison of mortality between <75- and ≥75-year-old patients revealed a statistical difference: 4.2 % versus 14.8 % ($p = 0.023$).

Conclusions Our study demonstrates that 30 % of idiosyncratic drug-induced agranulocytosis concerned elderly patients. Antibiotic, antithyroid, neuroleptic, anti-epileptic, and antiaggregant platelet agents are the primary causative drug classes. Idiosyncratic drug-induced agranulocytosis is typically serious in this frail population of elderly patients, with at least 50 % suffering from severe sepsis and with a mortality rate of approximately 15 %. Modern management of agranulocytosis may reduce the infection-related mortality (3.3 %).

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Key Points

More than one-third of idiosyncratic drug-induced agranulocytosis concerns elderly patients, with several co-morbidities and polymedication.

To date, the main causative drugs of idiosyncratic drug-induced agranulocytosis are: antibiotics, especially beta-lactams and sulfametoxazole; antithyroid drugs, particularly carbimazole; antiaggregant platelet agents, principally ticlopidine; and neuroleptics.

Despite the population's frailty and severity of the clinical manifestations, appropriate management of septic complications, using broad-spectrum antibiotic therapy and hematopoietic growth factors, may improve the prognosis of idiosyncratic drug-induced agranulocytosis.

1 Introduction

Idiosyncratic drug-induced agranulocytosis (IDIA) is historically characterized by neutrophil count $<0.5 \times 10^9$/L, impaired health, and severe mucositis [1]. This relatively rare disorder has an annual incidence of 2–15 cases/million [2]. While all drugs can be considered causes of IDIA, cotrimoxazole, antithyroid drugs, ticlopidine, and clozapine are currently the typical causes cited [3]. Although patients experiencing IDIA may initially be asymptomatic, the neutropenia often translates into the onset of severe sepsis depending on its severity [3, 4]. With appropriate management, the mortality rate of IDIA agranulocytosis is currently estimated at 5–10 % [2, 3].

Data on neutropenia in the elderly and agranulocytosis meeting the criteria of evidence-based medicine is currently scarce in the literature [5]. To our knowledge, the data that exists is patchy or non-existent in terms of IDIA. We have, however, conducted a preliminary study on this topic involving 25 elderly patients (>65 years old) [6].

In this paper, we report data on 61 patients aged over 75 years with established IDIA, followed up in a referral center within a university hospital.

2 Patients and Methods

2.1 Objective

The main objective of the current study was to describe the clinical picture and outcome of patients aged >75 years with established IDIA.

2.2 Patient Selection

All IDIA cases reported in patients hospitalized in the Strasbourg University Hospitals (a tertiary referral center) since the early 1990s were included in a prospective cohort study (partial data published in [7]). Patients were recruited from the Internal Medicine, Onco-Hematology, Geriatric Medicine, Rheumatology, and Digestive Surgery Departments. To date, more than 200 patients were included in this cohort study.

In the present study, we only studied elderly patients ≥75 years old.

The inclusion and exclusion criteria are listed in Table 1. All the cases fulfilled the international criteria of IDIA [2, 8]. All the cases also respond to the criteria: "*Vraisemblable*" (likely causative) and "*Très vraisemblable*" (very likely causative) of the French method for causality assessment of adverse drug reactions [9]. All IDIA cases were reported to the Regional Pharmacovigilance Center of Alsace, France.

2.3 Data Collected and Method

All data were obtained from patient files. For each case, the patient was seen by two members of the monitoring committee, with each of the following factors recorded (when available): age; gender; medical history and co-morbidities (such as diabetes mellitus, cardiovascular or respiratory disorders, renal failure, or systemic inflammatory disorders); clinical presentation; drugs administered (dose, route, start date, and withdrawal date); absolute white

Table 1 Criteria for inclusion in and exclusion from the study

Inclusion criteria
Patients had to fulfill the following conditions[a]
Neutrophil count $<0.5 \times 10^9$/L
Existence of fever and/or clinical infection and/or signs of septic shock (chills and sweating, collapse, confusion)
Fulfilled criteria standardized by Benichou et al.: onset of agranulocytosis during treatment or within 7 days in cases of previous intake of the same drug, no clinical features, and $>1.5 \times 10^9$/L neutrophils in blood cell count 1 month after drug interruption [8]
Exclusion criteria
History of congenital neutropenia or immune neutropenia
No features of recent viral infection[b]
Recent chemotherapy, radiotherapy, and/or immunotherapy
Existence or development of an underlying hematological disease

[a] For enrollment, patients had to be hospitalized (conventional hospitalization)

[b] All patients had negative serological tests for human immunodeficiency virus, hepatitis B and C virus, Epstein-Barr virus, cytomegalovirus, and parvovirus B19

blood cell, hemoglobin (Hb), and platelet counts; bone marrow analysis; clinical features; time to reach a neutrophil count exceeding 1.5×10^9/L (hematological recovery); use of hematopoietic growth factors (HGF), e.g. granulocyte-colony stimulating factor (G-CSF); number of days in hospital; final outcome, recourse to intensive care, and mortality rate.

All these variables have been mainly compared between patients <75 and ≥75 years. We also studied some of these variables (clinical presentation, recourse to intensive care, and mortality) in a group of patients aged ≥85 years.

2.4 Statistical Analysis

Data were expressed as mean and standard deviation (SD) and analyzed using the Mann–Whitney test and Student's *t* test for paired data. The distribution of quantitative variables was assessed graphically and using the Shapiro–Wilk test. Comparison of quantitative variables between the two groups was performed using the nonparametric Mann–Whitney test. The qualitative variables were presented as numbers and percentages, analyzed using Pearson's Chi-squared or Fisher's exact test, depending on the number of patients. A p value <0.05 was considered statistically significant. Analyses were performed using the R software (Version 3.2.2).

2.5 Administrative Data

All data were registered in the French national database of drug side-effects (*Réseau des Centres Régionaux de Pharmacovigilence* [*CRP*]). The data collected were subject to the French national data protection act (*Commission Nationale Informatique et Liberté)* (*CNIL*). This study received approval from the local ethics committee.

3 Results

From January 1990 to January 2014, 203 patients with IDIA were registered. Of the 203, 61 (30 %) were over 75 years old. One presented with two episodes of IDIA (related to two different drugs).

3.1 Patient Baseline Characteristics

Patient data are presented in Table 2. All patients were Caucasian. Mean and median ages were 84.9 and 82 years (range 75–95), respectively. The female/male ratio was 2.4.

Underlying disease (co-morbidity) was found in 74 % ($n = 45$), consisting of cardiac disorder (atrial fibrillation, arterial hypertension, myocardial infarction, arteritis of lower limbs, or stroke) ($n = 34$, 55.7 %); cardiac failure ($n = 8$, 13.1 %); renal failure ($n = 19$, 31.1 %); diabetes mellitus ($n = 8$, 13.1 %); chronic obstructive pulmonary disorder and respiratory insufficiency ($n = 4$, 6.5 %); systemic disorder like rheumatoid arthritis ($n = 1$, 1.6 %).

Table 2 Clinical characteristics of the patients and outcome according to age: <75 and ≥75 years old

	Patients <75 years old ($n = 142$)	Patients ≥75 years old ($n = 61$)
Mean age (years)	54.7	84.9
Gender-ratio F/M	1.2	2.4
Mean neutrophil count at diagnostis	$0.16 \pm 0.17 \times 10^9$/L	$0.15 \pm 0.17 \times 10^9$/L
Discovery circumstances		
Asymptomatic neutropenia	54.8 %	48.3 %
Isolated fever	45.2 %	36.7 %
Documented infections	0 %	13.3 %
Clinical features during hospitalization		
Asymptomatic neutropenia	11.6 %	3.4 %
Isolated fever	23.3 %	27.6 %
Documented pneumonia	15.5 %	20.7 %
Septicemia and septic shock	5.4 %	24.1 %
Other documented infections	44.2 % (with 27 acute tonsillitis [19 %])	24.1 % (with 4 acute tonsillitis [6.6 %])
Number of deaths	4.2 % ($n = 6$)	14.8 % ($n = 9$)[a]
Recourse to intensive care	17.1 %	17.5 %

[a] Only two of these deaths were related to infectious complications

3.2 Causative Drugs

A single drug was documented as "likely causative" or "very likely causative" in all except four cases (93.4 %), for which two to four drugs were suspected. The respective causative drugs were stopped during the first 48 h of admission in 37 patients (61.7 %).

The main drug families found to be causative were: antibiotics ($n = 25$, 43.8 %), especially β-lactams ($n = 16$) and cotrimoxazole ($n = 9$); antithyroid drugs ($n = 9$, 15.8 %); neuroleptic and anti-epileptic agents ($n = 7$, 12.3 %); antiaggregant platelet agents ($n = 6$, 10.5 %), especially ticlopidine ($n = 5$).

In two-thirds of cases, patients were treated with at least five drugs, (mean 5; range 1–13) (data available for $n = 41$). There was only one case of self-medication.

The mean duration of the suspected drug intake was 18 days (range 3–120). A quarter of the patients received the causative drug for at least 30 days.

3.3 Clinical Manifestations

The discovery circumstances were: decrease in neutrophil blood count ($n = 29$, 48.3 %); isolated fever ($n = 22$, 36.7 %); documented infections like acute tonsillitis or pneumonia ($n = 8$, 13.3 %); one case of septic shock (Table 2).

The clinical presentations during hospitalization were: isolated fever (unknown origin) ($n = 16$, 27.6 %); documented pneumonia ($n = 12$, 20.7 %); septicemia ($n = 9$, 15.5 %) or septic shock ($n = 5$, 8.6 %) (together 24.1 %) (data available for $n = 58$) (Table 2). The remaining symptomatic patients presented documented infection ($n = 14$, 24.1 %) such as acute pyelonephritis ($n = 4$); sore throat and acute tonsillitis ($n = 4$); cutaneous infection ($n = 1$); cholecystitis ($n = 1$); colitis ($n = 1$); infectious spondylitis ($n = 1$); endocarditis ($n = 1$); and fever with deep venous thrombosis ($n = 1$). Two patients (3.4 %) remained asymptomatic during hospitalization.

While in hospital, 15 patients (25.9 %) exhibited features of severe sepsis, septic shock, or systemic inflammatory response syndrome (SIRS).

Bacteriological documentation was obtained in 23 cases (42.6 %) (data available for $n = 54$), revealing 14 (60.9 %) Gram-positive cocci cases, primarily involving *Staphylococcus* ($n = 10$); nine (39.1 %) bacillus Gram-negative cases, principally *Escherichia coli* ($n = 4$) and *Pseudomonas aeruginosa* ($n = 4$). In one case, the bacterial infection was associated with a *Candida albicans* infection.

3.4 Hematological Data

At the time of suspected diagnosis, the mean and median neutrophil counts were 1.62 and 1.5×10^9/L (range 0.26–3.6). At the neutrophil decrease nadir, the mean and median neutrophil counts were 0.15 and 0.08×10^9/L (range 0–0.4) (Table 2). At total of 54 % of patients ($n = 33$) had neutrophil levels $<0.1 \times 10^9$/L.

Only 12 patients (20 %) exhibited isolated neutropenia. Anemia (Hb level <120 g/L) was documented in 76.7 % ($n = 46$). The mean Hb level was 107.1 g/L (range 47–146). Nine patients (15 %) had thrombocytopenia (platelet count $<100 \times 10^9$/L). The mean platelet count was 220×10^9/L (range 7–694).

Bone-marrow analysis (data available for $n = 36$) primarily detected myeloid hypocellularity with apparent cessation of myeloid precursor maturation (in the promyeloid stage) in 77.8 % of cases ($n = 28$).

3.5 Outcome and Duration of Hospitalization

Outcome was favorable in 85.3 % of subjects; nine patients died (Table 2). Two elderly patients (85 and 92 years old) died of uncontrolled septic shock due to *Pseudomonas aeruginosa* and extensive bilateral pneumonia, respectively. Seven additional mortalities with several co-morbidities were caused by acute cardiac failure ($n = 4$), hemorrhage stroke ($n = 1$), and massive pulmonary embolism ($n = 1$). In one patient, the cause of death was not determined. Three of these eight patients were treated with G-CSF.

The mean and median durations for hospitalization (available for 38 patients) were 40.4 and 21 days (range 5–180), respectively. Seven patients (17.5 %) required intensive care (data available for $n = 40$) (Table 2).

All patients also received, immediately and as first line, broad-spectrum parenteral antibiotic therapy when exhibiting any sepsis features, often piperacillin or cefotaxime in association with netromycin or amikacin, except in cases of beta-lactam allergy or beta-lactam-induced agranulocytosis. The mean and median durations for antibiotic therapy (data available for $n = 27$) were 21.1 and 15 days (range 7–120), respectively.

Eight of the anemic patients (17.4 %) required blood transfusion. Notably, no patient required white blood cell transfusion.

3.6 Duration of Hematological Recovery and Response to Hematopoietic Growth Factors

The mean and median durations of hematological recovery (neutrophil count $\geq 1.5 \times 10^9$/L) were 7.2 and 6 days (range 2–20), respectively. The mean and median durations for neutrophil count $\geq 0.5 \times 10^9$/L were 6.7 and 5 days (range 1–24), respectively.

G-CSF (administered subcutaneously in a fixed dose of 300 μg/day) was given to 36 patients (59 %), particularly those with neutrophil counts $<0.1 \times 10^9$/L, severe clinical features of infection (e.g., collapse, septicemia, or extensive pneumonia) or unstabilized underlying disease. This HGF was administered for a mean duration of 4.5 days (range 1–9).

In these 36 patients, the mean duration of hematological recovery was significantly reduced to 6.1 days (range 2–16) ($p = 0.039$); that of antibiotic therapy and hospitalization were not significantly reduced (data not developed).

3.7 Comparison of Patients According to Age

A comparison of patient clinical pictures and outcome according to age, i.e. <75 and ≥75 years old, is presented

in Table 2. Our comparison of discovery circumstances and clinical manifestations during hospitalization revealed no statistical difference between <75- and ≥75-year-olds (all $p > 0.3$). Comparison of the neutrophil count at diagnosis also revealed no statistical difference between the two age groups ($p = 0.21$). In contrast, comparison of neutrophil count at nadir demonstrated a statistical difference between the groups, with deeper neutropenia observed in patients ≥75 years old ($p = 0.04$). Significantly, comparison of mortality between the <75- and ≥75-year-old groups revealed a statistical difference: 4.2 % versus 14.8 % ($p = 0.023$).

Nineteen patients older than 85 years have been included in the present study. The mean age of these patients was 88.4 years. The mean neutrophil count was $0.2 \pm 0.19 \times 10^9$/L. During hospitalization, these very elderly patients had the same clinical pictures as the group ≥75 years with: isolated fever (15.4 %); documented pneumonia (46.2 %), and other documented infections (39.4 %). In this age group, the mortality rate was 21.1 % ($n = 4$) and recourse to the intensive care unit was 26.3 % ($n = 5$). All four deaths were related to co-morbidities.

4 Discussion

To our knowledge, this is the first study of elderly patients over 75 years of age with documented IDIA. Defining IDIA remains a controversial issue [2, 3]. Several authors require criteria of the Schultz historic definition [1] or a neutrophil count 0.1×10^9/L [8, 10]. Our patient diagnoses were in agreement with the definition proposed by Benichou et al. and the International Agranulocytosis and Aplastic Anemia Study (IAAAS) [8, 11] (Table 1). All patients exhibited unquestionable agranulocytosis: mean and median neutrophil counts of 0.15 and 0.08×10^9/L (range 0–0.4) at the neutrophil decrease nadir; clinical features of sepsis with life-threatening infections (e.g., extensive pneumonia, septicemia, or septic shock) in 25 % of cases; microbial documentation in 42.6 %. In all cases, the principal diagnostic criterion for IDIA, namely complete hematological recovery following removal of the causative drug, was fulfilled (except in the two who died). As IDIA is a life-threatening condition, no patient was re-challenged with the incriminated drug ('theoretical method of reference').

This study highlights the emergence of classical causative drugs: antibiotics (43.8 %), especially beta-lactams and sulfamethoxazole; antithyroid drugs (15.8 %), particularly carbimazole; antiaggregant platelet agents (16 %), principally ticlopidine; and neuroleptics. We have previously reported some of these findings in an unselected elderly population over 90 years of age [7]. Our data were in accordance with those published by Shapiro et al. [12] and van der Klauw et al. [13, 14].

As described by Fattinger et al., we also found, especially in elderly patients, that poly-medication was a predisposing factor for IDIA [15], yet self-medication was not. We observed that two-thirds of our patients received at least five drugs, whereas there was only one case of self-medication.

The clinical features of IDIA in our population of elderly patients did not differ from those of other series including patients of all ages [3, 4]. More than one-quarter of the patients did not develop symptoms related to IDIA at all during the observation period. These asymptomatic patients were those with the shortest duration of neutropenia. However, severe infections (e.g., septicemia, shock, extensive pneumonia, cutaneous cellulitis or deep infection) were more frequent in our patients, i.e. in at least 50 % of cases, probably due to the study design enrolling solely hospitalized patients (for details, see Sect. 2). Over 25 % of our patients presented features of severe sepsis, septic shock, and/or SIRS, and 17.5 % required intensive care. Only two (3.4 %) remained asymptomatic during hospitalization.

As demonstrated in Table 2, comparison of clinical features during hospitalization according to age (<75 and ≥75 years old) appears to reveal no significant differences.

IDIA is a life-threatening disorder at any age, as well as in elderly subjects presenting with several co-morbidities. It has a mortality rate of 5–20 % [16]. In a previous study involving 90 patients (all ages), we established a mortality rate of >5 % [7]. In the elderly patients, a mortality rate of 14.7 % was found. Nine patients died, yet only two elderly patients (85 and 92 years old, respectively) died of sepsis in relation to agranulocytosis, namely uncontrolled septic shock due to *Pseudomonas aeruginosa* and extensive bilateral pneumonia, respectively.

In our present study, seven additional patients died of uncontrolled co-morbidities. Note that our population here was elderly (mean age: 84.9 years) and that 74 % of the patients presented with underlying diseases that were often not stabilized, especially cardiac and renal disorders. In the Julia et al. study, these latter criteria (old age [>65 years] and renal failure) were poor prognostic indicators as evidence of severe infections, in association with a neutrophil count $<0.1 \times 10^9$/L [4].

Comparison of the number of deaths and recourse to intensive care appears to demonstrate differences according to age: 4.2 % and 17.1 % in <75-year-olds versus 21.1 and 23.1 % in ≥85-year-olds, respectively. Comparison of mortality between <75- and ≥75-year-olds revealed a statistical difference ($p = 0.023$). Maloisel et al. have also previously documented the negative impact of co-morbidities and old age in a cohort of 91 patients [17].

We believe our patients share many similarities with frail patients. This probably contributed to, besides our significant observed mortality, the longer hospitalizations of our patients, with a mean duration >40 days.

Notably, our data suggests that, despite the population's frailty and severity of the clinical manifestations, appropriate management of septic complications of IDIA, especially using broad-spectrum antibiotic therapy and HGF, may improve the prognosis [3, 18]. Only two deaths directly resulted from sepsis, compared to severe neutropenia. In our center, all patients received established care procedures (for details, see [2, 7]). In our opinion, this may account for our good results (mortality <15 %).

Remarkably, faster hematological recovery (neutrophil count $>1.5 \times 10^9$/L) was observed in the HGF group: 6.1 versus 7.2 days ($p = 0.039$). Nevertheless, we observed no other improvements in these elderly patients associated with HGF therapy, particularly relating to duration of antibiotic therapy and hospitalization. These results are consistent with those reported in recent larger studies of HGF therapy in adult IDIA patients [18–20]. The only available prospective randomized study (based on 24 patients with antithyroid-related IDIA) did not confirm the benefit of G-CSF [21]. In our opinion, this negative result may be related to inappropriate G-CSF doses (100–200 μg/day) [2].

Our study had several limitations. Primarily, the data originated from a population covering a period of over 20 years. Thus, there may be heterogeneity concerning the causative drug and perhaps the management process. Moreover, all the patients were referrals.

On the other hand, our study exhibits several strengths. It was the first to investigate IDIA in elderly patients, with established and documented IDIA. In addition, this study was conducted in a single center, with experienced physicians particularly accustomed to managing neutropenia and agranulocytosis.

5 Conclusion

In conclusion, our study demonstrated: that 30 % of IDIA cases concern elderly patients; that antibiotic, antithyroid, neuroleptic and anti-epileptic, and antiaggregant platelet agents are the mainly implicated drug classes; that IDIA is typically serious in this frail population of elderly patients, with at least 50 % exhibiting severe sepsis and a mortality rate of approximately 15 %; and that modern management of IDIA may reduce the infection-related mortality.

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Compliance with Ethical Standards

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