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Idiosyncratic Agranulocytosis in Elderly Patients

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Few data, meeting the criteria of evidence-based medicine, are currently available in the literature on neutropenia in the elderly [1]. To our knowledge, these data are patchy or non-existent in case of idiosyncratic drug-induced acute neutropenia or agranulocytosis (IDIA). In the present paper, we report our experience of elderly patients with established IDIA.

From January 1990, all elderly patients with IDIA, older than 75 years, hospitalized at the Hopitaux Universitaires de Strasbourg (Strasbourg, France, a tertiary referral center), were registered. All the cases fulfill the international criteria of IDIA [2].

Sixty-one patients were identified. One patient presented 2 episodes of IDIA (with 2 different drugs). All patients were Caucasian. The mean and median ages were 84.9 and 82 years (range, 75-95), respectively. The sex-ratio female/male was 2.4. Seventy-four percent of the patients (n=45) presented an underlying disease. Main families of causative drugs were: antibiotics (n=25, 43.8%), especially ß-lactams (n=16) and cotrimoxazole (n=9); antithyroid drugs (n=9, 15.8%); neuroleptic and anti-epileptic agents (n=7, 12.3%); and antiaggregative platelet agents (n=6, 10.5%), especially ticlopidine (n=5). There was only 1 case of self-medication. Discovery circumstances were (n=60): decrease in neutrophil blood counts (n=29, 48.3%); isolated fever (n=22, 36.7%); documented infections (n=8, 13.3%), as acute tonsillitis or pneumonia, with one case of septic shock. Clinical presentations during hospitalization were (n=58): isolated fever (fever of unknown origin) (n=16, 27.6%); documented pneumonia (n=12, 20.7%); septicemia (n=9, 15.5%); septic shock (n=5, 8.6%). The remaining symptomatic patients presented documented infections (n=14, 24.1%), as: acute pyelonephritis (n=4); sore throats and acute tonsillitis (n=4); cutaneous infections (n=1); cholecytitis (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 the hospitalization. During the hospitalization, 15 patients (25.9%) presented features of severe sepsis, septic shock and/or systemic inflammatory response syndrome (SIRS). Bacteriological documentation (n=54) was obtained in 23 cases (42.6%). At the time of discovery, the mean and median neutrophil counts were 1.62 and 1.5 × 10^9/L (range, 0.26-6.3). At nadir of the neutrophil decrease, mean and median neutrophil counts were 0.15 and 0.08 × 10^9/L (range, 0-0.4). Fifty-four percent of patients (n=33) had neutrophil levels of less than 0.1 × 10^9/L.

The outcome was favorable in 85.3% of subjects; nine patients died. Two elderly patients (85 and 92 years old) died of uncontrolled septic shock due to *Pseudomonas aeruginosa* and extensive bilateral pneumonia, respectively. Seven additional patients with several comorbidities died of: acute cardiac failure (n=4), hemorrhage stroke (n=1) and of massive pulmonary embolism (n=1). In one patient, the cause of death was not determined. Three of these 8 died patients were treated with G-CSF. Comparison of the clinical characteristics of the patients and the outcome according to the age (≥ 75 years old; ≥ 85 years old) are presented in Table 1.

	Patients ≥ 75 years (n=61)	Patients ≥ 85 years (n=19)
Mean aged (years)	84.9	88.4
Sex-ratio F/M	2.4	2.8
Mean neutrophil count at diagnostic	0.15 ± 0.17 × 10^9/L	0.2 ± 0.19 × 10^9/L
Discovery circumstances	-Asymptomatic neutropenia: 48.3%	-Asymptomatic neutropenia: 47.4%
	-Isolated fever: 36.7%	-Isolated fever: 31.6%
	-Documented infections: 13.3%	-Documented infections: 21%
Clinical features during hospitalization	-Asymptomatic neutropenia: 3.4%	-Isolated fever: 15.4%
	-Isolated fever: 27.6%	-Documented pneumonia: 46.2%
	-Documented pneumonia: 20.7%	-Other documented infections: 39.4%
	-Septicemia and septic shock: 24.1%	

	-Other documented infections: 24.1% (with 4 acute tonsillitis [6.6%])	
Number of death	14.8% (n=9)[*]	21.1% (n=4)[**]
Recourse to an intensive care unit	17.50%	23.10%
[*]: only 2 of these deaths were related to infectious complications; [**]: all these 4 deaths were related to comorbidities		

Table 1: Clinical characteristics of the patients and the outcome according to the age (<75 years old; ≥ 75 years old; ≥ 85 years old).

To our knowledge, this is the first large study of elderly patients older than 75 years with documented IDIA. This work highlights the emergence of new causative drugs, such as: antibiotics, especially betalactam and sulfametoxazole; antithyroid drugs, particularly carbimazole; antiaggregative platelet agents, principally ticlopidine; and neuroleptics. The clinical features of IDIA in our population of elderly patients did not differ from other series including patients of all ages [3,4]. However, we have more likely severe infections (e.g., septicemia, shock, extensive pneumonia, cutaneous cellulite or deep infections) in at least 50% of our cases, probably because of the study design with only enrollment of hospitalized patients. In our elderly patients, a mortality rate of 14.7% has been found. Nine patients have died but only 2 elderly patients (85 and 92 years old) died of sepsis in relation to the agranulocytosis. They died of uncontrolled septic shock due to *Pseudomonas aeruginosa* and extensive bilateral pneumonia, respectively. In our center, all patients were managed with an established procedure [2,5]. To our opinion, an explanation of our good results (mortality <15%) may be due to this measure.

References

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