Case report

Polyserositis in the course of chronic myelomonocytic leukemia: impact of hypomethylating agents.

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Abstract

Chronic myelomonocytic leukemia (CMML) is a rare myelodysplastic/myeloproliferative neoplasm (MDS/MPN) disorder with frequent extra-hematopoietic manifestations. CMML-related serositis is due to leukemic involvement, autoimmune manifestations or both. Serositis is correlated to adverse outcome in the course of CMML in small case-series reported before the introduction of hypomethylating agents into the clinical practice. We report a favorable evolution of 3 patients with CMML and polyserositis treated by Azacytidine.

Key words: CMML, Azacytidine, hypomethylating agents, serositis, cardiac tamponade

Introduction

Chronic myelomonocytic leukemia (CMML) is defined by absolute monocytosis (more than $1x10^9$/l) in the peripheral blood persisting at least 3 months and by dysmyelopoiesis. Clonal evolution to acute myeloid leukemia occurs in 15-20% of patients. Treatment options are limited, including supportive care, chemotherapy and hypomethylating agents (1). Stem cell transplantation could be proposed to young patients. In CMML, systemic and autoimmune complications are commonly encountered (2). However, pleural and/or pericardial manifestations are barely reported.

Case Presentation

We report here three patients with CMML and polyserositis (Table 1). (1) A 70-year-old man with CMML-1 had stable disease during 6 years. He was referred for progressive dyspnea and chest pain. Chest X-rays revealed a pleural effusion and echocardiography showed a

Table 1. Clinical and biological characteristics of the patients.

P	Age	Sex	WBC	Mono	Blasts	Karyo	Treat.	F. up	status
#1	70	M	64	11	2%	46,XY	HU / azacytidine	17 month	Alive
#2	68	F	50	11	3%	46,XX	HU / azacytidine	6 month	Alive
#3	70	M	6.9	2	5%	-Y	azacytidine	38 month	Alive

Age in years; Blasts: bone marrow blast percentage; F: female; F.up: follow-up from therapy; HU: hydroxyurea; Karyo: oncologic karyotype; Mono: monocytes count ($x10^9$/l); M: male; P: patients; Treat: treatments; WBC: white blood count ($x10^9$/l).

circumferential pericardial effusion without features of cardiac tamponade. Routine blood tests were: hemoglobin 91g/l, platelet count $94x10^9$/l and white blood cell count (WBC) $64x10^9$/l including $11,2x10^9$/l monocytes. C-reactive protein (CRP) was 140,9mg/l. Treatment by colchicine and aspirin was started but after one week, the patient experienced acute respiratory distress due to massive left pleural effusion. Pleural drainage disclosed an exusudative sterile pleural fluid that contained 39g/l proteins, $3,5x10^9$/l cells (presence of 80% neutrophils) without evidence for leukemic infiltration. Although microbiological cultures were negative, broad-spectrum antibiotherapy was given without changes in pulmonary infiltrates. Due to an acute respiratory distress syndrome and progressive leukocytosis, treatment with hydroxyurea was given. Hence, patient's clinical condition gradually improved allowing mechanical ventilation weaning after 2 weeks. Bone marrow biopsy showed features of CMML-1. Treatment with hypomethylating agent (Azacytidine) started 3 month after the onset of respiratory symptoms. The patient is free of cardiac and respiratory symptoms one year after azacytidine onset. At this point, blood tests are normal except for a moderate increase in the monocytes count ($4x10^9$/l) and bone marrow examination show the persistence of dysplasia on the myeloid and monocytic lineages. (2) A 68-year-old woman was admitted for dyspnea and chest pain. CT-scan showed a minimal bilateral pleural effusion. Echocardiography revealed a circumferential pericardial effusion without cardiac tamponade. Blood tests were: hemoglobin 84g/l, WBC $50x10^9$/l including $11x10^9$/l monocytes and platelets $208x10^9$/l. Bone marrow biopsy was consistent with CMML-1. Pleural fluid was a sterile exsudate that contained 39g/l proteins and $1,54x10^{12}$/l cells including $1x10^{12}$/l monocytes, suggestive of a specific pleural involvement by CMML. CRP was 284mg/l. Treatment by hydroxyurea was started due to a rapid increase of WBC mostly constituted of mature monocytes. Capillary-leak syndrome (diffuse oedema, urticaria-like rash with non-specific dermal oedema and increased volume of pleural and pericardial effusions) prompted the initiation of hypomethylating agent therapy by Azacytidine. One month later, all the symptoms had resolved, CRP was 2mg/l and WBC was $1,7x10^9$/l including $0,2x10^9$/l monocytes, hemoglobin was 112g/l and platelets were $636x10^9$/l and patient condition remains stable upon Azacytidine therapy with a 6-month follow-up. While complete blood count (CBC) returned in the normal values, bone marrow examination showed the persistence of myeloid cell dysplasia. (3) A 70-year-old man was referred for acute respiratory distress and chest pain. Chest X-rays revealed bilateral pleural effusion and echocardiography showed a cardiac tamponade requiring emergency surgical pericardiocentesis and pleural drainage.

Table 2. Reports of serositis in CMML patients.

1st Author	Y	N	A	S	L/Mo (B)	Site	Karyo	Chemo	St	FU	Ref.
Mufti	1984	1	82	F	68/20	Pl/*	46,XX	RA	CR	10m	(8)
		2	59	M	39/19	Pl	46,XY	RA	CR	12m	
		3	61	F	46/43 (5)	Pl	-22q	HU/RA/Eto	CR	12m	
		4	82	F	53/9.5	Pl/As	46,XX	CY/RA	Died [1]	8w	
Manoharan	1991	1	52	F	87/23 (4)	Pl/*	-7q - 20q	6TG/CY/Eto	Died [2]	4m	(9)
Bradford	1993	1	60	M	16/4.5 (5)	Pl/Pc/As/*	46,XY	CY/Eto/CTC	Died [3]	10m	(10)
Mani	1994	1	77	F	126/47 (2)	Pc/*	ND	HU	CR	2.5y	(11)
		2	60	M	71/25 (1)	Pc	ND	HU/Eto	CR	3y	
		3	69	F	129/70	Pl/Pc	ND	HU	Died [4]	2w	
		4	81	F	100/50 (10)	Pc	ND	HU	Died [5]	2d	
Bourantas	1998	1	54	F	14/4.2	Pl/Pc/*	ND	CTC	CR	-	(12)
		2	67	M	13/52 (20)	Pl/*	ND	CY	Died [6]	2w	
		3	70	F	18/4.5	Pl/*	ND	CTC/HU	CR	-	
		4	70	M	26/6.5	Pl/*	ND	CTC	CR	-	
Strupp	2000	1	70	F	27/11 (15)	Pl/Pc/*	46,XX	HU	Died [7]	2w	(13)
Watanabe	2004	1	68	M	-	Pl	-	HU/Eto	Died [8]	3m	(14)
Yamazaki	2005	1	61	M	(14)	Pl	46,XY	HU	CR	-	(15)
Morita	2011	1	64	F	13/3.2 (9)	Pl/Pc	46,XX	HU/Eto	Died [9]	2w	(16)
Imataki	2014	1	63	F	24/6.7 (1)	Pl	Tri(1)	HU/CTC	CR	14m	(17)

Causes of death: [1] stomach carcinoma; [2] sepsis; [3] disease progression; [4] acute myeloid leukemia; [5] sepsis; [6] sepsis; [7] respiratory distress; [8] perforative peritonitis; [9] respiratory distress.
A: age in years; As: ascites; (B): bone marrow blast percentage; Chemo: chemotherapy; CR: complete remission of serositis; d: days; F: female; FU: follow-up; Karyo: karyotype; L: leukocytes; M: male; Mo: monocytes; m: month; N: number of patients; Pc: pericardial involvement; Pl: pleural involvement; S: sex; St: status; w: weeks; y: years; Y: year of publication; * : spleen, liver and/or lymphe nodes enlargement.
Type of chemotherapies: CTC: corticosteroids; CY: cytarabine; Eto: etoposide; HU: hydroxyurea; RA: dexrazoxane; 6TG: 6-thioguanine.

Pleural and pericardial fluids were sterile and revealed the presence of 60% neutrophils and 40% lymphocytes. Blood tests were: hemoglobin 110g/l, WBC 6,9x10^9/l including 2x10^9/l neutrophils and 2,1x10^9/l monocytes and platelet count was 128x10^9/l. CRP was 240mg/l. Bone marrow biopsy showed CMML-1. Treatment by Azacytidine started in the peri-operative period and the clinical and biological evolution was favorable including normalization of CRP. The patient received 24 cycles of Azacytidine with repeated normal chest X-rays and echocardiography. During follow-up, CBC and CRP were normal and features of CMML remained present on repeated bone marrow examinations. Azacytidine was ultimately

stopped due to painful skin reactions and fatigue, and follow-up test remained unchanged one year after treatment discontinuation.

Discussion

CMML shares features of both myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) (3) and may present with liver or/and spleen enlargement and lymphadenopathy (4). Infiltration of soft tissues including skin, gingiva, cartilage or central nervous system and serous effusions are infrequent (4). From our best knowledge, pleural and pericardial effusions were previously reported in only 19 cases in CMML (Table 2). In most cases, specific pleural (16/19) and/or pericardial (8/19) involvement by CMML was identified, usually associated with other CMML-involved sites including spleen, liver and/or lymph nodes. Ascites was found in only 2 cases and was probably CMML-unrelated in one case (perforative peritonitis). In our 3 patients, we found both pleural and pericardial involvement may be due to extensive search using CT-scan and echocardiography. Management of CMML-related serositis appeared variable but involved chemotherapy in all excepted 2 cases in which pleural and pericardial effusions were sensitive to single-agent corticosteroids (Table 2). We report here for the first time the use of hypomethylating agents in CMML-related serositis. The initial management of our three patients diverged particularly regarding the timing of specific therapy initiation. However, we avoided the use of steroids in all of them at any step of their treatment, suggesting that their clinical evolution was mostly due to a specific activity against CMML. We thus believe that Azacytidine participated to the early control of leukemic infiltration, inflammation and autoimmunity that contributed to polyserositis and allowed long-term remission of effusions. In fact, mechanisms underlying serous effusions in CMML remain elusive. Association between CMML and autoimmunity is increasingly recognized while pathogenic mechanisms are barely studied. Increased cytokines production by monocytes including TNFα, Interleukin-6 or IRF1 (interferon regulatory factor-1) were suggested to trigger B-lymphocytes polyclonal proliferation, antibodies production, abnormal antigen presentation and global deregulation of immune response (5, 6). Polyserositis was associated to an increased C-reactive protein (CRP) level in our three patients, which might suggest the involvement of interleukin 6 (IL-6) in the pathophysiology of CMML-related serositis. In two of our patients, no evidence for CMML serous involvement was found – which was more frequent compared to reported cases (Table 2). In these cases, the implication of an immune-mediated process may be hypothesized, suggesting that in future studies, B- and T-cell functions analysis as well as plasma and pleural cytokine measurements should be conducted to decipher the mechanisms of serositis in this context. In polyserositis-associated CMML, as in other systemic or autoimmune manifestations of CMML, hypomethylating agents should be considered to control the underlying myeloid clone involved in systemic symptoms rather than using immunosuppressive drugs (7). Based on reported cases, polyserositis may adversely affect CMML outcome as 9/19 (47%) patients died few weeks after diagnosis and only one of these patients had evidence for acute myeloid leukemia transformation (Table 2). Among our 3 patients, none of them had standard criteria for hypomethylating agent therapy initiation regardless their systemic symptoms (1) and during the follow-up we did not found evidence for clonal evolution even if features of CMML were still present in repeated bone marrow examinations. In CMML patients with lower than 10% of bone marrow blast cells experiencing severe systemic symptoms such as polyserositis, we suggest that the use of hypomethylating agents may represent a safe option with activity towards the systemic inflammatory reaction.

Conclusion

Our current results suggest that treatment with hypomethylating agents is safe and result in long-lasting responses in CMML-associated polyserositis. Treatment duration should be clarified in the absence of oncologic reason for therapy initiation and should probably be adapted to effusion mechanisms, i.e. month-long in the absence of leukemic infiltration versus until disease progression in case of specific serous involvement. Ideally, these therapeutic options should be investigated prospectively in clinical trials involving CMML patients with extra-hematological complications. Moreover, mechanisms underlying systemic and autoimmune complications of MDS remain mostly unknown and represent a very attractive field for future basic and translational investigations.

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