Case report

Behçet's disease, myelodysplastic syndrome, trisomy 8, gastroenterological involvement – An association

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ABSTRACT

Only a limited number of cases of Behçet's disease and hematological malignancies have been reported in the literature. We report the case of a 45 year old female patient with Behçet's disease who developed myelodysplastic syndrome, refractory anemia with excess blasts in transformation subtype, with complex chromosomal abnormalities, including excess of chromosome 8, following several years of treatment with chlorambucil for Behçet's disease. As has been described in most such cases, gastrointestinal involvement was most prominent. This case is described and the occurrence of myelodysplastic syndrome in Behçet's disease reviewed.

Introduction

Behçet's disease is an inflammatory disorder of unknown etiology, characterized by recurrent oral and genital ulceration, arthritis, ophthalmic and skin lesions. Involvement of the intestines, central nervous system, other visceral organs and vascular system can also occur (1). In addition to colchicine and low dose steroids, Behçet's disease patients are often treated with immunosuppressive therapy, such as azathioprine, and occasionally drugs like chlorambucil and cyclosporine A. Current therapy options also include alpha-interferon and anti-TNF agents (2-3).

Only a limited number of cases of Behçet's disease and hematological malignancies, all lymphomas, have been reported in the literature (4-8), except for an unlikely cluster of patients with an association of myelodysplastic syndrome (MDS) and Behçet's disease.

We present the case of a patient with Behçet's disease who developed myelodysplastic syndrome which evolved to secondary acute leukemia following immunosuppressive treatment, review the literature and discuss the relevant issues.

Case report

A 45 year old female patient, first presented to the rheumatology clinic in 1995 with persistent arthritis of both ankles and knees as well as erythema nodosum. She reported rheumatic symptoms on and off for 15 years, but no details or medical records were available. An evaluation of her arthritis, including evaluation of inflammatory bowel disease was unrevealing. She was treated with low dose steroids, hydroxychloroquine and colchicine. The symptoms were controlled with this regimen.

In January 1997, while under therapy, the patient presented with a flare of her disease: oral and genital ulceration, erythema nodosum and disabling arthritis of multiple upper and lower extremity joints. The cardiovascular, respiratory, abdominal and ophthalmologic examinations were unremarkable. Initial laboratory work revealed antinuclear antibodies, rheumatoid factor negative; C3 and C4 normal. A pathergy test was not performed.

The diagnosis of Behçet's disease was made (9) and the patient treated with increased steroids. Attempts at treatment with methotrexate, sulfasalazine, cyclosporine A and azathioprine failed due to adverse reactions. As the patient continued to suffer from non-scarring, intractable oral and genital ulcers and arthritis and required high dose steroids for control, treatment with chlorambucil 4 mg per day was initiated.

From 1998 to the end of 2003 her disease was managed in the community and controlled under a regimen of chlorambucil 4 mg/d, colchicine 1 mg/d

and prednisone 15 mg/d. Repeated blood counts were normal.

In September 2003, treatment with colchicine and chlorambucil was withdrawn due to pancytopenia. The patient was asymptomatic at that time. The course of her disease, laboratory tests and treatments from this point are summarized in Table I. The patient returned to the hospital 2 weeks later with an upper respiratory tract infection. Her temperature was normal. The blood count showed persistent pancytopenia. Chest and sinus X rays were interpreted as normal. Antibiotic treatment with cefuroxime was started.

Two weeks later the patient was admitted to the hospital suffering from severe watery diarrhea, abdominal pain and fever, 38°C, still under prednisone 20 mg/d. Abdominal and chest X ray were interpreted as normal. Stool culture grew Campylobacter jejuni. The patient was treated with azythromycin with relief of her symptoms and fever. A week later, while still under treatment, her condition deteriorated with profuse watery diarrhea and abdominal pain, this time accompanied by polyarthritis and oral and genital ulceration with a fever of 39°C. Laboratory work revealed worsening of pancytopenia, hypokalemia, hypoalbuminemia, CRP-494 mg/l (normal less than 6 mg/ml) and positive occult blood in the stool. Small bowel series showed multiple filling defects in the ileum, suggestive of ulceration. Due to her poor general condition an endoscopic evaluation was not performed. A bone marrow aspiration and biopsy established the diagnosis of myelodysplastic syndrome, FAB subtype-refractory anemia with excess of blasts.

Treatment with broad spectrum antibiotics, pipracillin-tazobactam, gentamycin, metronidazole later replaced by meropenem, vancomycin, and amphotericin B was ineffective. She was resuscitated with IV fluids, electrolyte replacement and blood transfusions. All blood, urine and stool cultures were negative for bacteria, viruses and parasites. As the patient's condition continued to deteriorate under the treatment, her symptoms could be attributed to a flare of Behçet's disease, possibly related to progressing MDS. She was treated with intravenous pulse methylprednisolone 1 gr/d with only transient improvement in her condition. A short term trial of treatment with infliximab also failed.

A second bone marrow biopsy was interpreted as Refractory Anemia (RA) with excess of blasts, in transformation to acute leukemia. Bone marrow chromosome analysis showed complex chromosomal abnormalities: 55,XX,-5q-,+i(8q),+i(8q),+11,+13,+14,+19,+22,+X,+dm. Due to her poor general condition and uncontrolled Behçet's disease she was not felt to be a candidate for chemotherapy treatment for her progressing MDS.

Despite intensive treatment the patient's condition deteriorated and she died with multi-organ system failure.

Discussion

The association of Behçet's disease with malignancies has rarely been reported, and even less so with hematolo-

Table I. Summary of the patient's terminal illness.

Clinical picture	Treatment
30/9/2003 Asymptomatic pancytopenia (Hb 9, WBC 2.5, PLT76)*	Colchicine and chlorambucil stopped
↓	
13/10/2003 Upper respiratory tract infection Pancytopenia (Hb 8.8, WBC 2.1, PLT90) Sinus and chest x-ray normal	Cefuroxime Tx Observation
↓	
3/11/2003 GI symptoms, fever Pancytopenia (Hb 7.6, WBC 3, PLT30) Stool culture – *C. jejuni*	Azythromycin Tx Prednisone dose increased
↓	
10/11/2003 GI symptoms, fever, arthritis, oral and genital ulcers Pancytopenia + electrolyte abnormalities	Pipracillin-tazobactam + gentamycin + metronidazol
Small bowel passage – filling defects	↓
Bone marrow biopsy – RAEB	Vancomycin + meropenem + Ampho B IVpulse steroids
↓	
20/11/2003 No response Blood, urine, stool cultures – negative	IVsteroids, IVinfliximab
↓	
5/12/2003 Clinical and laboratory deterioration Bone marrow biopsy – RAEB-t	Blood products and supportive care
↓	
20/12/2003 Patient died with multi-organ system failure.	

*WBC x 10^9/L; Hb in mg/dL; PLTx 10^9/L.

gical malignancies. We present a case of Behçet's disease in association with MDS in transformation to acute leukemia, which raises a number of issues: the relationship of MDS to Behçet's disease and the role of gastrointestinal involvement and chromosome abnormalities there in.

The association of MDS and immunological abnormality disorder has been well described in the literature. Clinical manifestations of such phenomena may include systemic vasculitic syndrome, skin vasculitis, fever, arthritis, inflammatory bowel disease and even classical connective tissue disorders (10). The prevalence of these manifestations among MDS patients has been estimated at between 10-18.5% (11-12). MDS associated with vasculitis has been reported to affect mostly cutaneous vessels or joints. The literature also includes case reports on Takayasu's arteritis (13), Henoch-Schonlein purpura (14) and other vasculitic syndromes.

The association between malignant diseases and Behçet's disease has not been widely investigated. The present literature suggests an increased risk of malignancies in connective tissue diseases, with a more marked increment in dermatomyositis and mixed connective tissue disease and a slight increase in systemic lupus erythematosus, rheumatoid arthritis and polymyositis reported (15-17). The autoimmune nature of the diseases and the immunosuppressive drugs used in their management are regarded as underlying this association. In reference to Behçet's disease and malignancy the literature is sparse. Cengiz *et al.* reported on 13 patients with only 3 of the patients having hematological malignancies (18).

Notably, most of the cases of Behçet's disease and hematological malignancy reported in the literature are of MDS. Until now, 26 patients with this association have been reported in the literature (19-38). Their main clinical and laboratory findings are summarized in Table II together with those of the current study patient. Most of the patients reported are from Japan. Their median age is 45 years, range 10-74. The majority of the patients had oral and genital ulcers, gastrointestinal (GI) symptoms, fever and skin lesions. Eye lesions and arthritis were infrequently reported. MDS was diagnosed before or concomitantly with Behçet's in most of the patients. Only one patient whose MDS was diagnosed after Behçet's disease received immunosuppressive (chlorambucil and cyclosporine) treatment before the diagnosis.

Whereas trisomy 8 has been the most common chromosomal abnormality reported in MDS associated with Behçet's disease, 18 out of 23 patients investigated, its reported incidence is only 10-20% among untreated general MDS patients with chromosomal abnormalities (39). Thus the percentage of trisomy 8 in MDS patients with Behçet's disease is markedly higher than in patients with MDS alone. In addition considering the high frequency of trisomy 8 in this setting with associated GI manifestations, Shinya *et al.* suggested that trisomy 8 might predispose patients with MDS and Behçet's disease to intestinal ulceration (33).

GI involvement of Behçet's disease typically affects the ileocecal region and colon. The frequency of GI involvement varies in different countries, with a lower frequency in Israel (14-25%) (40) as compared to Japan (50-60%) (41). Our patient's severe GI involvement, unusual for her locale, dovetails well with the patients reviewed in the literature who had prominent GI symptoms when MDS was present with Behçet's disease.

Although the relationship between trisomy 8 and GI manifestations of Behçet's disease is reported frequently in the literature, as stated above, the mechanism of this relationship remains unclear. Shinya suggested that the presence of trisomy 8 facilitates cytokine production in both lymphocytes and supporting tissues and that their elevated level may result in the findings (33). Another proposed mechanism related to an increase in reactive oxygen species (ROS) production. In Behçet's disease there is increased production of ROS by activated neutrophils and these functions may be increased in the subgroup of MDS patients with trisomy 8 and thus may play an important role in the complications associated with Behçet's disease and MDS (26).

A relationship between malignancies and immunosuppressive treatment in rheumatic diseases has been demonstrated in studies (42). Specifically an increased risk of malignancies of the immune system, lymphoma and multiple myeloma, has been observed in rheumatic disease patients treated with azathioprine as compared to untreated patients (43). Other studies, have observed an increased risk of leukemia in rheumatoid arthritis patients treated with chlorambucil (44). A causal relationship between alkylating agents, such as chlorambucil and secondary malignancies, in general, is well established (45). These agents form DNA cross links that interfere with replication, repair and translation of DNAand may thus be mutagenic.

There is evidence in the literature that the use of immunosuppressive drugs is associated both with chromosomal abnormalities as well as with myelodysplastic syndrome (47-48). Le Beau *et al.* reported a series of patients with therapy-related MDS, 97% of them demonstrating chromosomal abnormalities, 87% with abnormalities of chromosome 5 and/or 7 (48). Our patient also had deletion of the long arm of chromosome 5 (del 5q). It has been suggested that the cytogenetic abnormalities induced by the drugs are more important than the mere prolonged use of immunosuppressive therapy in the pathogenesis of MDS. Due to the complex chromosomal abnormalities in our patient it is not possible to infer clear causality between the immunosuppressive therapy and development of MDS in the present case.

In summary, we present a case of a woman with Behçet's disease who developed pancytopenia, diagnosed as MDS, after immunosuppressive treatment of her underlying condition. Cytopenias are common in patients with rheumatic diseases and may be the consequence of varying etiologies. Prior immunosuppressive treatment should raise the possibility of evolving secondary hematological malignancy. In Behçet's disease, the peculiar association with MDS, trisomy 8 and gastrointestinal involvement is highlighted.

Table II. Clinical characteristics of 27 patients with Behçet's disease associated with myelodysplastic syndromes.

Case	Age/ sex	Country	Karyotype	MDS classification	Symptoms	Disease diagnosed first	Cytotoxic Tx prior to MDS	Outcome	Ref.
1	50/F	Korea	46XX-8-20+der(8) t(8;20) (p23;q10)	RA	IOGA	B	----	Stable	19
2	ND/M	Japan	47XY+8	RA	OSG	M		ND	20
3	67/M	USA	ND	ND	IOGSA	M		Stable	22
4	ND	Japan	+8	ND	IOSGT	M		ND	24
5	ND	Japan	+8	ND	IOSGT	M		ND	24
6	41/F	Japan	47XX+8	RARS	IOS	M+B		Stable	21
7	23/F	Japan	47XX +8	RA	IOGS	M		Improved	23
8	54/F	Japan	47XX +8	RA	OGS	M		Death	23
9	39/M	Japan	47XY+8	RA	IOG	B	----	Stable	25
10	34/F	Japan	47XX+8	RA	IOGU	M		Stable	26
11	39/F	Germany	45XX-7	RAEB-t	IOGUS	B	Chlorambucil, cyclosporine	Death	27
12	35/M	Japan	46XY	RA	OSGA	M		Stable	28
13	57/M	Japan	47XY+8	RA	IOG	M		Stable	28
14	52/M	Japan	47XX+22,t(9;22) (q34;q11)	RA	OSA	M		Stable	28
15	72/M	Japan	47XY+8,del(20)(q11)	RA	OG	M		Improved	29
16	59/M	Japan	43XY-5,-7,48,-16,-18 -20,3p-,7q+,12p-	RAEB-t	OTAUN	M		Death	30
17	45/F	Japan	48XX+8,+15	RARS	OGS	M+B		Stable	31
18	57/M	Japan	ND	RARS	OS	M		ND	32
19	74/F	Japan	45X,-X,+i(5)(p10),+del (7)(q21;q32), +8,-9,+13 ,-17,-18,-20,-22	RA	IOT	M+B		Died	33
20	36/F	Japan	47XX,dup(1)(q12;q44),+8	RA	IST	M+B		Died	33
21	31/F	Japan	47XX+8	RA	IT	B	-----	Died	33
22	56/M	Spain	ND	RAEB	IOG	B+M		ND	34
23	10/F	Japan	ND	ND	I	B+M		Stable following CBT	35
24	27/F	Japan	47XX,+8	RAEB	OGS	B	-----	Stable following CBT	36
25	56/F	Japan	47XX,+8	RA	IOGS	B	-----	Stable	37
26	50/M	Italy	47XY,+8	RARS	I	B		Death	38
27	54/F	Israel	55,XX,5q-,+i(8q),+11,+13,+14, +19,+22,+X	RAEB-t	IOGSA	B	Chlorambucil	Death	this case

I: intestinal involvement; O: oral ulcer; G: genital ulcer; S: skin lesion; U: uveitis; A: arthritis; T: thrombosis; N: neuropathy; B: Behçet's disease; M: myelodysplastic syndrome; ND: not done.

References

1. SAKANE T, TEKENO M, SUZUKI N, INABA G: Behçet's disease. *New England Journal of Medicine* 1999; 341: 1284-91.
2. MARSHALL SE: Behçet's disease. *Best Pract Res Clin Rheumatol* 2004;18:292-311.
3. FRENCH-CONSTANT C, WOLMAN R, JAMES DG: Cyclosporin in Behçet's disease. *Lancet* 1983;I I :454-5.
4. KAWAMOTO S, TERADA H, NIIKURAH, KUMASAKA T, SAIKI S: Hodgkin's disease associated with Behçet's disease. *Rinsho Ket - sueki* 1992; 33: 211-5.
5. ABE T, YACHI A, YABANA T *et al.*: Gastric non-Hodgkin's lymphoma associated with Behçet's disease. *Intern Med* 1993; 32: 663-7.
6. KATSURA Y, SUZUKAWA K, KOJIMA H *et al*.: Cytotoxic T cell lymphoma arising in Behçet's disease. *Int J Hematol* 2003; 77: 282-5.
7. YAMAMOTO T, TAMURA M, HAMAUZU T *et al.*: Intestinal Behçet's disease associated with Non-Hodgkin's lymphoma. *J Gastroen - terol* 1997; 32: 241-5.
8. HOUMAN MH, BEN GHORNEL I, MILED M: Intestinal lymphoma associated with Behçet's disease. *Ann Med Interne* 2001 152: 415-8.
9. INTERNATIONAL STUDY GROUP FOR BEHÇET'S DISEASE: Criteria for diagnosis of Behçet's Disease. *Lancet* 1990; 335: 1078-80.
10. VOULGARELIS M, GIANNOULI S, RITIS K, TZIOUFAS AG: Myelodysplasia-associated autoimmunity: clinical and pathophysiologic concepts. *Eur J Clin Invest* 2004;34:690-700.
11. GIANNOULI S, VOULGARELIS M, ZINTZARAS E, TZIOUFAS G, MOUTSOPOULOS HM: Autoimmune phenomena in myelodysplastic syndromes: a 4-yr prospective study. *Rheumatology* 2004; 43: 626-32.
12. CASTRO M, CONN DL, SU WP, GARTON JP: Rheumatic manifestations in myelodysplastic syndromes. *J Rheumatol* 1991; 18: 721-7.
13. AMBERGER C, DENZLINGER C, JANZEN J, MULLER-SCHIMPFLE M, MOHREN M, KOTTER I: Takayasu's arteritis secondary to myelodysplasia as a predictor of poor outcome: Two case reports. *Clin Exp Rheum* 2004; 22: 346-8.
14. BLANCO R, GONZALEZ-GAY MA, IBANEZ D *et al*.: Henoch-Schonlein purpura as clinical presentation of a myelodysplastic syndrome. *Clin Rheum* 1997; 16: 626-8.
15. BLACK KA, ZILKO PJ, DAWKINS RL, ARMSTRONG BK, MASTAGLIA GL: Cancer in connective tissue disease. *Arthritis Rheum* 1982; 25: 1130-3.
16. BARNES BE, MAWR B: Dermatomyositis and malignancy: a review of the literature. *Ann Intern Med* 1976; 84: 68-76.
17. CANOSO J, COHEN AS: Malignancy in series of 70 patients with SLE. *Arthritis Rheum* 1974; 17: 383-8.
18. CENGIZ M, ALTUNDAG MK, ZORLU AF, GULLU IH, OZYAR E, ATAHAN IL: Malignancy in Behçet's disease: A Report of 13 cases and a review of the literature. *Clinl Rheumatol* 2001; 20: 239-44.
19. OH EJ, YOON JS, PARK YJ, CHO CS, KIM BK: Behçet's disease associated with myelodysplastic syndrome: A case report. *J Korean Med Sci* 1999; 14: 685-7.
20. NAWATA R, SHINOHARA K, TAKAHASHI T, YAMADA T, KATSUKI K: Refractory anemia

with trisomy 8 complicated by Behçet's disease with elevated levels of inflammatory cytokines. *Rinsho Ketsueki* 1999; 40: 1100-1104.
21. CHYUMA Y, UTSUNOMIYA A, SAITO T, HANADAS, NISHIMATA H, ARIMA T: Hemolytic anemia complicated with Behçet's disease and myelodysplastic syndrome. *Rinsho Ketsueki* 1992; 33: 333-7.
22. KARUVANNUR S, LIPSTEIN E, ROSNER F: Atypical Behçet's disease in a patient with myelodysplastic syndrome. *Mt Sinai J Med* 2001; 68: 403-5.
23. YANO K, EGUCHI K, MIGITA K *et al*.: Behçet's disease complicated with myelodysplastic syndrome report of two cases and review of the literature. *Clin Rheumatol* 1996; 15: 91-3.
24. OGAWA H, KURODA T, INADA M *et al*.: Intestinal Behçet's disease associated with myelodysplastic syndrome with chromosomal trisomy 8: a report of two cases and review of the literature. *Hepatogastroenterology* 2001; 48: 416-20.
25. TANAKA E, NISHINARITA M, UESATO M, KAMATANI N: A case of intestinal Behçet's disease with abnormal ossification complicated by myelodysplastic syndrome, symptoms revealed after the perforation of ileum ulcer. *Ryumachi* 2000; 40: 711-8.
26. OHNO E, OHTSUKA E, WATANABE K *et al.*: Behçet's disease associated with myelodysplastic syndromes. *Cancer* 1997; 79: 262-8.
27. BANGERTER M, GRIESSHAMMER M, V TIRPITZ C *et al.*: Myelodysplastic syndrome with monosomy 7 after immunosuppressive therapy in Behçet's disease. *Scand J of Rheumatol* 1999; 28: 117-9.
28. NAKAYAMA S, ISHIKAWA T, YABE H, NAGAI K: Refractory anemia complicated by Behçet's disease. *Rinsho Ketsueki* 1989; 3 530-4.
29. NESHASHI Y, TORII Y, YAGUCHI M, ITOH Y, OHAYASHIKI K, TOYAMA K: Incomplete Behçet disease in a case of monopathic myelodysplastic syndrome presenting as thrombocytopenia. *Rinsho Ketsueki* 1988; 29: 1097-102.
30. TAKASHITA N, HORIUCHI T, HATO T, FUJITA S, KOBAYASHI Y: Myelodysplastic syndrome complicated with Behçet's disease. *Ehime Igaku* 1991; 11: 39-43.
31. YOSHIZAWA Y, HIRAI A, IZAKI S, KITAMURAK: Behçet's disease associated with myelodysplastic disorder. *Hifu Rinsyo* 1992; 34: 1585-9.
32. KEGEYAMA H. HIDAKA T, KONDO S, TAMARU K: Intestinal Behçet's disease associated with myelodysplastic syndrome. *Rinsho Ketsueki* 1993; 34: 1288.
33. SHINYA K, KIMURAS, KURODA J *et al*.: Trisomy 8 involved in myelodysplastic syndrome as a risk factor for intestinal ulcers and thrombosis – Behçet's disease. *Leukemia and Lymphoma* 2001; 42: 115-21.
34. MOLINA M, AGUAYO JL, ORTEGA G, DE PACO M, CUESTA F, AGUADO MD: Non-specific digestive ulcers and Behçet's disease. *Annales de Medicina Interna* 1992; 9: 237-38.
35. YAMATO K: Successful cord blood stem cell transfusion for myelodysplastic syndrome with Behçet's disease. *Int J Hematol* 2003; 77: 82-5.
36. TOMONARI A, TOJO A, TAKAHASHI T *et al.*: Resolution of Behçet's disease after HLA-mismatched cord blood transplantation for myelodysplastic syndrome. *Ann Hematol* 2004; 83: 464-6.
37. HASEGAWA H, IWAMASAK, HATTA N, FUJITA S: Behçet's disease associated with myelodysplastic syndrome with elevated levels of inflammatory cytokines. *Modern Rheumatol* 2003; 13: 350-5.
38. DELLA ROSSA A, TAVONI A, TOGNETTI C, BOMBARDIERI S: Behçet's disease with gastrointestinal involvement associated with myelodysplasia in a patient with congenital panhypopituitarism. *Clin Rheum* 1998; 17: 515-7.
39. SOLE F, PRIETO F, BADIA L, WOESSNER S, FLORENSA L, SANS-SABRAFEN J: Cytogenetic studies in 112 cases of untreated myelodysplastic syndromes. *Cancer Genetics and Cytogenetics* 1992; 64: 12-20.
40. KRAUSE I, MADER R, SULKES J, PAUL M, UZIEL W, ADAWI M, WEINBERGER A: Behçet's disease in Israel: the influence of ethnic origin on disease expression and severity. *J Rheumatol* 2001; 28: 1033-6.
41. BAYRAKTAR Y, OZASLAN E, VAN THIEL D: Gastrointestinal manifestation of Behçet's disease. *J Clin Gastroenterol* 2000; 30: 144-54.
42. ASTEN P, BARRETT J, SYMMONS D: Risk of developing certain malignancies is related to duration of immunosuppressive drug exposure in patients with rheumatic diseases. *J Rheumatol* 1999; 26: 1705-14.
43. MATTESON E, HICKEY A, MAGUIRE L, TILSON H, UROWITZ M: Occurrence of neoplasia in patients with rheumatoid arthritis enrolled in DMARD registry. *J Rheumatol* 1991; 18: 809-14.
44. PATAPANIAN H, GRAHAM S, SAMBROOK PN *et al*.: The oncogenicity of chlorambucil in rheumatoid arthritis. *Br J Rheumatol* 1988; 27: 44-7.
45. GERSON S: Molecular epidemiology of therapy related leukemias. C*urr Opin Oncol* 1993; 5: 136-44.
46. RYFFEL B: The carcinogenicity of cyclosporin. *Toxicology* 1992; 73: 1-22.
47. CONOR J, SHELDON S, MCCUNE J: Cytogenetic abnormalities and therapy-ralated myelodysplastic syndromes in rheumatic disease. *Arthritis Rheum* 1988; 41: 1493-6.
48. LE BEAU MM, ALBAIN KS: Clinical and cytogenetic correlation in 63 patients with therapy-related myelodysplastic syndromes and acute non-lymphocytic leukemia: further evidence for characteristic abnormalities of chromosomes no. 5 and 7. *J Clin Oncol* 1986; 4: 325-33.