Infectious Mononucleosis: the Prognostic Significance of Various Changes of the Blood Leukocytes

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INFECTIOUS MONONUCLEOSIS received its descriptive name in 1920 when Sprunt and Evans[1] recognized the characteristic changes in the peripheral blood. Before this time the terms, "glandular fever,[2, 3] acute idiopathic lymphadenitis,[4] monocytic angina[5]" and "acute benign lymphoblastosis,[6]" had been used to describe a clinical picture which seemed appropriate to each designation. Because of the lack of specific diagnostic methods and the confused terminology, interest in the disease temporarily waned. However, since the work of Downey and McKinlay[7] and Bunnell[8] this void has been largely filled.

The recognition of the characteristics of the abnormal cells in the peripheral blood in infectious mononucleosis was a significant step forward in our knowledge of this disease. These abnormal cells were noted early in the 1920's[1, 6, 9, 10] and distinguished from those seen in leukemia, but it was not until Downey and McKinlay's[7] classic work in 1923 that the cytologic details were fully described. Many observers had considered these cells to be "monocytes" while others spoke of them as immature lymphocytes. Downey showed that, in general, these cells were mature and well differentiated. Heck[11] has reviewed this early work on morphology, and the reader is referred to this paper and Downey and McKinlay's original publication[7] for a full description.

In a recent study of 210 sporadic cases observed at the Mayo Clinic from January 1, 1937 to January 1, 1947, it was found that in 96.6 per cent, smears of the peripheral blood showed a significant increase in atypical lymphocytes characteristic of infectious mononucleosis.

In half of these cases cytologic changes in the lymphocytes characteristic of this disease were noted by the eighth day of illness. The average time in all cases was fourteen days despite the fact that in 109 instances an average of twelve days elapsed from onset of symptoms until the patients sought medical attention. Serial smears were not made, but it is possible that had they been made, most or all of the remaining patients would have shown the characteristic blood picture at some time during the illness.

In an attempt to ascertain what, if any, prognostic significance the leukocytes found in smears of the peripheral blood might have, the relationship of the onset and clinical course to the cytologic changes of the leukocytes was studied in 25 cases. These cases were placed in four groups as follows: (1) acute onset with severe clinical course, 7 cases; (2) acute onset with mild clinical course, 6 cases; (3) insidious onset with severe clinical course, 6 cases; and (4) insidious onset with mild clinical course, 6 cases. The clinical course was considered to be mild if the symptoms were negligible, fever was absent or of low grade and the dura-

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tion was not unduly protracted. Conversely the course was considered to be severe when the systemic reaction was pronounced and protracted, fever high, pharyngitis and adenitis extensive. One patient in this group actually succumbed in the fifteenth day of his illness.

The group selected had either a positive blood smear or a positive heterophil agglutination test or both in addition to compatible clinical findings. The heterophil agglutination test (performed in the Division of Clinical Laboratories) was

TABLE 1.—*Acute Onset with Severe Clinical Course*

Case	Age, yr. and sex	Leukocyte count*	Day of disease	Differential count, per cent								Heterophil		Lymphocytes, no. per 100					Duration of illness, days
				Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils	Metamyelocytes	Myelocytes	Promyelocytes	Titer	Day obtained	Normal	Type I	Type II	Type III	Predominating type	
1	17M	9,700	9	34.5	63	2.5			0	0	0	1:1,792	9	32	36	22	10	I	12+
2	11M	23,600	2	Toxic 23.5	75.5	1		1	0	0	0	1:448	5	14	8	36	42	III	11
3	29M	4,600 4,300 16,700 18,700 6,100	5 7 15 19 23	49 32	36 55	13 10	2 2	1				1:3,584	13	6	14	70	10	II	27
4	16F	10,100 8,300	7 30	Toxic 39	59.5	1					0.5	1:5,120	8	28	8	58	6	II	30
5	21F	9,700 19,200 6,100	3 5 30	Toxic 26	68	3			2		1	1:1,792	3	24	64	8	4	I	30
6	21F	6,800 4,800	2 41	71 46	26 47	3 5	2					1:224	68	31	14	54	1	II	68+
7	21M	13,800	12	39	48	8			4	1		Not done		14	18	62	6	II	15† died

* Per cu. ml. of blood.

† Disease was fulminating, bronchopneumonia had supervened at time of death.

considered suggestive of infectious mononucleosis when the titer was 1:112 and positive when the titer was 1:224 or more. In this group of 25 cases, the data given show that in 1 case the test was not performed and in another the titer was not found above 1:112. A blood smear was assumed to be positive for infectious mononucleosis when 50 per cent or more lymphocytes appeared in the differential count among which half were atypical lymphocytes of infectious mononucleosis.

In each case, careful study of the morphologic features of the leukocytes was made. This included: (1) a differential leukocyte count; (2) a differential count

of 100 lymphocytes noting the ratio of normal lymphocytes to atypical lymphocytes of infectious mononucleosis and the relative proportion in the latter of each of the three types described by Downey and McKinlay[7]*; (3) a search for granulocytic immaturity; (4) observation of toxic changes in the granulocytes; and (5) shift to the left of the neutrophils.

Observations

Lymphocytes of all types characteristic of infectious mononucleosis constituted 50 per cent or more of all the lymphocytes in each case. The type of lymphocyte of infectious mononucleosis described by Downey which predominated apparently bore no relation to the severity of the clinical course. Of the 25 patients selected for study 14 were found to have type I lymphocytes predominating;

Table 2.—*Acute Onset with Mild Clinical Course*

Case	Age, yr. and sex	Leukocyte count*	Day of disease	Differential count, per cent								Heterophil		Lymphocytes, no. per 100					Duration of illness, days
				Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils	Metamyelocytes	Myelocytes	Promyelocytes	Titer	Day obtained	Normal	Type I	Type II	Type III	Predominating type	
8	21M	12,400	10	14.5	77.5	3.5	2	1		1	0.5	1:2,560	12	13	16	62	9	II	18
9	25M	10,600	1	37	55	7	1					1:1,792	10	13	72	13	2	I	15
		6,000	10	22	65	13													
10	17F	6,500	15	32	60	8						1:896	17	16	73	8	3	I	21
11	6M	21,800	3	30	61	7.5	1.5					1:224	3	12	74	13	1	I	15
12	8F	11,900	10	22	67	9		1			1	1:448	13	18	54	28		I	14
13	17F	15,400	8	11	82.5							1:224	11	16	71	13		I	17
		8,800	11			5													

* Per cu. ml. of blood.

10 were found to have type II predominating; and 1, for whom a diagnosis of leukemia was originally entertained, was found to have type III cells predominating (tables 1 to 4).

Of the 16 patients who had some type III lymphocytes of infectious mononucleosis, 11 (about 69 per cent) had had an acute onset of the condition. How-

* Type I leukocytoid lymphocytes contain an indented or lobulated, often eccentric, nucleus with a coarse chromatin mesh, abundant, usually deeply basophilic and vacuolated cytoplasm. The nuclei of type II lymphocytes are generally centrally situated and coarser than type I nuclei. The cytoplasm is more abundant and appears almost as a frill around the nucleus as areas of pale and deeply basophilic cytoplasm alternate. Among type III leukocytoid lymphocytes the cytoplasm retains most of the features seen in type I lymphocytes, but the nucleus is larger, contains nucleoli and is leukemic in appearance.

TABLE 3.—*Insidious Onset with Severe Clinical Course*

Case	Age, yr. and sex	Leukocyte count*	Day of disease	Differential count, per cent								Heterophil		Lymphocytes, no. per 100				Predominating type	Duration of illness
				Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils	Metamyelocytes	Myelocytes	Promyelocytes	Titer	Day obtained	Normal	Type I	Type II	Type III		
14	17F	11,800 5,200	14 36	33 36	62 51	5 8	3	2				1:1,280	20	22	34	44		II	13 wk.
15	8F	3,500 14,000	5 10	26 5.5	66 93	4 1.5	4					1:3,584	11	12	66	20	2	I	24 da.
16	25F	9,100 9,100	56 180	27.5	68	3	0.5	1				1:112 1:112	56 70	10	44	46		II	6 mo.
17	21F	16,500	60	24	68.5	5.5			0.5	0.5	1.0	1:1,792	61	10	80	2	8	I	80 da.
18	29M	9,700 13,300	10 13	17	64	8			11			1:448	12	32	52	16		I	35 da.
19	26M	14,200 18,700	14 16	13	77	6.5			3.5			1:1,792	14	4	40	56		II	18 wk.

* Per cu. ml. of blood.

TABLE 4.—*Insidious Onset with Mild Clinical Course*

Case	Age, yr. and sex	Leukocyte count*	Day of disease	Differential count, per cent								Heterophil		Lymphocytes, no. per 100				Predominating type	Duration of illness, days
				Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils	Metamyelocytes	Myelocytes	Promyelocytes	Titer	Day obtained	Normal	Type I	Type II	Type III		
20	12F	10,200 5,800	10 30	15 67	78 27	1.5 5	1 1	0.5	2	1	1	1:896	11	40	32	26	2	I	18
21	15F	13,700 7,100	15 35	22 44	77 51.5	 3	0.5 1	0.5 0.5				1:320	15	30	18	52		II	35
22	21F	13,000 7,200	8 13	40 38	55 57	2 4	2 1	1				1:896	9	22	26	51	1	II	15
23	18F	4,300	3	41	39	15	5					1:896	9	50	40	9	1	I	10
24	4F	12,200	5	22	69	9						1:448	17	34	46	20		I	30
25	21F	10,150 5,700	7 15	30 25	69 68	 6	1 1					1:448	21	30	43	27		I	21

* Per cu. ml. of blood.

ever, a mild course was as frequent as a severe stormy course irrespective of the presence of these cells.

Granulocytic immaturity to the early myelocyte was observed in the periph-

eral blood in 6 cases. In 4 of these 6, the onset of the disease was acute. A moderate shift to the left of the neutrophils was observed; however, this was not constant. Significant "toxic" changes in the granulocytes were seen in only 3 of the 25 cases. However, in all 3 the course was severe.

Comment

It is interesting to note that Downey and McKinlay,[7] in their original paper, reported only 1 case in which type III lymphocytes characteristic of infectious mononucleosis were present, and then they were not numerous. Limarzi and coworkers[12] noted them but rarely in their series. In our study, type III lymphocytes were encountered in 16 of the 25 cases (64 per cent), although they were preponderant in only 1 case.

That 69 per cent of the patients having type III lymphocytes were among those in whom the onset was acute, suggests a relationship between the type of onset and the occurrence of these cells. The number of cases involved here, however, is too small for it to be more than suggestive. There was no apparent correlation between the appearance of these cells and morbidity. Neither was there any correlation of type I and type II lymphocytes with the clinical course of the infectious mononucleosis.

With type I lymphocytes predominating in 56 per cent of our 25 cases of infectious mononucleosis, type II predominating in 40 per cent, and with type III in only 4 per cent, the rate of occurrence of these types in our series is similar to that of Downey and McKinlay[7] who listed them by type in order of frequency.

Summary

Peripheral blood smears were studied in 25 selected cases of infectious mononucleosis. In 7 the onset was acute and the course severe, in 6 the onset was acute and the course mild, in 6 the onset was gradual and the course severe, and in 6 the onset was gradual and the course mild. The predominance of any of the various types of lymphocytes of infectious mononucleosis was not noted to bear any relationship to the clinical course, although type III lymphocytes and granulocytic immaturity may be more frequently seen when the onset is acute. When toxic changes are present in the granulocytes, the clinical course is likely to be severe.

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