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The Metastatic Spread of Myeloma and Leukemias in Men

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Summary. This investigation was based on the analysis of 580 autopsy records of patients with plasma cell myeloma or any type of leukemia. The data were collected by the Department of Pathology at Roswell Park Memorial Institute between 1956 and 1965.

The primary purpose of this paper was to elucidate the metastatic process in myelomas and different types of leukemia. Two mutually exclusive hypotheses were tested, i.e. whether the spread of a cancer from the primary tumor throughout the body was due to a simple diffusion or if a cascade process took place.

The basic definition of the "cascade or multistep" diffusion of cancer is that it takes place in steps; that is, at least one intermediate step is usually required for the disease to progress from the primary tumor to generalized dissemination throughout the body.

It appeared that either the liver or spleen are the two major diffusing sites; that is, no generalized metastasis occurs unless the spleen and/or liver are seeded first.

Introduction

The primary purpose of this paper is to elucidate the process of metastases in myelomas and different types of leukemia by the methods previously developed for the study of metastatic processes in solid tumors and sometimes called "cascade analysis". The basic idea of cascade analysis is that the dissemination of metastases is ordinarily a multistep or cascade process rather than a simple diffusion from the primary site. That is, at least one intermediate step is usually required for the disease to progress from localization in the primary site to generalized dissemination through the body, and the purpose of cascade analysis is to determine the sequence of steps involved in the process. For the solid tumors previously studied [7], widespread metastases rarely occurred unless metastasis had occurred to certain key sites ("generalizing sites"), but this pattern would not necessarily apply for malignancies which were not solid tumors. In what follows, the cascade sequences for myeloma and leukemias will be described.

Methods and Material

This investigation is based on 580 autopsy records on patients with plasma cell myeloma or any type of leukemia which were collected by the Department of Pathology at Roswell Park Memorial Institute between 1956 and 1965. These records were a part of a computerized file of 4,728 autopsy records collected by Dr. John Pickren, Chief of Pathology, and archived by the Department of Biostatistics.

Each autopsy record includes age at time of diagnosis, sex, diagnosis by site and by histology, approximate survival time and detailed description of the presence or absence of

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metastases at 47 sites. Summary counts are obtained for two systems, the central nervous system and the endocrine system.

All of the primary sites considered in this paper belong to the bone marrow. They include plasma cell myeloma, chronic lymphocytic leukemia, acute lymphocytic leukemia, chronic myelocytic leukemia and acute myeloblastic leukemia. The term "metastases" will be used here in speaking about the dissemination of these diseases. This may be an awkward terminology for those pathologists or internists who do not like to use this word in connection with leukemia, because the process may not be exactly analogous to the process for solid tumors. Unfortunately there does not seem to be any generally accepted alternative name for the process. The major metastatic sites considered as possible generalizing sites were those organs when the proportion of cases with metastatic involvement was highest. For the bone marrow primaries, a preliminary analysis indicated that the major metastatic sites were the spleen and the liver, to a less extent, the lungs and the kidney. Metastases to the central nervous system and to the endocrine system were considered as indicators of generalized disease.

The principal sites in the chain of events connecting the primary site with generalized metastatic disease, the sequence of the sites and the role of the sites in the overall process, was determined by the statistic methods of cascade analysis. These are described in more detail in Appendix I. The statistical procedure is a relatively simple and straightforward one in which (1) the pertinent 2×2 tables for the occurrences of metastases at different sites are produced, (2) the direction of the seeding, if there is a direction, is determined by using the Sign Test for the cells where one site is positive but not the other, (3) the extent of the effect is determined by a Chi-square Test on the 2×2 table. In most cases the data give a clearcut and unambiguous specification of the cascade sequences when this procedure is applied.

Results

In Table 1 it appears that the overwhelming majority of the sign tests are significant at a 5% probability level. The metastatic route is from the spleen to the lungs via the liver. This conclusion is evident because the counts of metastases in the off diagonal cells of the tables are quite different from each other.

No directional metastases could be detected between the spleen and the liver in the plasma cell myeloma; a sequence of metastatic routes from the spleen to the liver is suggested in chronic lymphocytic leukemia, although not significant at a 5% probability level.

The study of the metastatic process was extended to the kidney (Table 4). The suggested metastatic path, after comparing only two organs, i.e. the lungs vs. the kidney, liver vs. kidney and spleen vs. kidney, appeared to be from the kidney to the lungs and from the spleen to the kidney and from the liver to the kidney. Sometimes a metastatic sequence was suggested by the data, although the sign test may not have been significant. The other half of Table 4 compares metastases in the kidney vs. metastases in the spleen with and without metastases in the liver.

None of the sign tests were significant in the plasma cell myeloma. The metastatic path could be either from the spleen to the kidney or from the liver to the kidney (suggested path).

In the acute lymphoblastic leukemia, it seems that the metastatic diffusion goes from the spleen to the kidney in presence of liver metastases (Table 4 and 5). The association of metastases in the spleen and kidney became significant at 5% probability level in presence of liver metastases. (chi-square = 6.24) (Table 5).

Table 1. Sets of 2 × 2 tables (presence or absence of metastases in paired organs) by different type of histology. (Chi-squares applied to the off diagonal elements, i.e. presence of metastases only at one site)

Histology		Liver −	Liver +	Chi-square	Spleen −	Spleen +	Chi-square
Plasma cell myeloma	Lung −[a]	58	17	15.06*	56	18	13.47*
	Lung +[b]	0	3		1	1	
Acute lymphoblastic leukemia	Lung −	39	22	8.04*	25	31	23.76*
	Lung +	6	25		2	29	
Chronic lymphocytic leukemia	Lung −	4	21	19.05*	5	16	11.53*
	Lung +	0	22		1	15	
Acute myeloblastic leukemia	Lung −	85	35	15.72*	61	51	38.47*
	Lung +	8	65		4	66	
Chronic myelocytic leukemia	Lung −	23	22	20.05*	10	23	16.00*
	Lung +	0	20		2	14	

Histology		Spleen −	Spleen +	Chi-square
Plasma cell myeloma	Liver −	47	10	0.05
	Liver +	10	10	
Acute lymphoblastic leukemia	Liver −	34	39	26.88*
	Liver +	4	51	
Chronic lymphocytic leukemia	Liver −	2	1	0.80
	Liver +	4	30	
Acute myeloblastic leukemia	Liver −	69	45	32.65*
	Liver +	4	92	
Chronic myelocytic leukemia	Liver −	9	9	2.08
	Liver +	3	28	

* Chi-square significant at a probability level below 5% (sign test).
[a] − = Absence of metastases at specific site.
[b] + = Presence of metastases at specific site.

In this instance, the cascade dissemination of metastases seems to require two organs, the spleen and the liver.

In chronic lymphocytic leukemia, the metastatic path seemed to go from the liver to the kidney. There was no increase between metastases in the spleen and kidney in presence of metastases in the liver (Table 5).

In the acute myeloblastic leukemia, the path is from the spleen to the kidney via the liver. The association of metastases in the spleen and kidney is much higher when metastases are present in the liver (chi-square = 9.19 vs. chi-square of 0.06) (Table 5).

In chronic myelocytic leukemia, the metastatic spread from the spleen to the kidney does not imply the presence of metastases in the liver (no change in the association of metastases in kidney and spleen in presence or absence of metastases in the liver) (Table 5).

Table 2. Sets of 2 × 2 tables (presence or absence of metastases in paired organs with or without metastases at third site) by different type of histology. (Chi-squares applied to the off diagonal elements, i.e. presence of metastases only at one site)

Histology		Liver −		Chi-square	Liver +		Chi-square	Spleen −		Chi-square	Spleen +		Chi-square
		SPL −	SPL +[c]		SPL −	SPL +		LI −	LI +[d]		LI −	LI +	
Plasma cell myeloma	Endocrine −[a]	43	9	1.23	6	7	0.36	43	6	0.10	9	7	3.13
	Endocrine +[b]	4	1		4	3		4	4		1	3	
Acute lymphoblastic leukemia	Endocrine −	29	10	1.07	3	13	8.64*	29	3	0.13	10	13	5.36*
	Endocrine +	5	29		1	38		5	1		29	38	
Chronic lymphocytic leukemia	Endocrine −	2	1	0.00	2	9	3.27	2	2	0.50	1	9	7.11*
	Endocrine +	0	0		2	21		0	2		0	21	
Acute myeloblastic leukemia	Endocrine −	60	18	2.37	3	28	23.31*	60	3	2.08	18	28	0.00
	Endocrine +	9	27		1	64		9	1		27	64	
Chronic myelocytic leukemia	Endocrine −	6	6	0.44	1	11	4.92*	6	1	0.25	6	11	3.50
	Endocrine +	3	3		2	17		3	2		3	17	

Histology		Lungs −		Chi-square	Lungs +		Cni-square	Spleen −		Chi-square	Spleen +		Chi-square
		SPL −	SPL +		SPL −	SPL +		LU −	LU +[e]		LU −	LU +	
Plasma cell myeloma	Endocrine −	48	15	1.57	1	1	0.00	48	1	4.00*	15	1	0.25
	Endocrine +	8	3		0	0		8	0		3	0	
Acute lymphoblastic leukemia	Endocrine −	22	17	8.45*	2	6	4.17*	22	2	0.00	17	6	2.45
	Endocrine +	3	14		0	23		3	0		14	23	
Chronic lymphocytic leukemia	Endocrine −	4	8	4.00*	0	2	0.00	4	0	0.00	8	2	2.50
	Endocrine +	1	8		1	13		1	1		8	13	
Acute myeloblastic leukemia	Endocrine −	55	26	11.28*	2	20	13.14*	55	2	1.12	26	20	0.36
	Endocrine +	6	25		2	46		6	2		25	46	
Chronic myelocytic leukemia	Endocrine −	7	12	4.27*	0	5	0.57	7	0	1.33	12	5	1.56
	Endocrine +	3	11		2	9		3	2		11	9	

* Chi-square significant at a probability level below 5% (sign test).

[a] − = absence of metastases at specific site.

[b] + = presence of metastases at specific site.

[c] SPL = spleen.

[d] LI = liver.

[e] LU = lungs.

In Table 2, the sign tests are significant when metastases are present at two major metastatic sites, i.e. liver and spleen. This remark holds true for the acute lymphoblastic and myeloblastic leukemias, acute and chronic myelocytic leukemia.

The suggested metastatic path is from the spleen (Table 2 and 5) to the endocrine system or from the liver to the endocrine system in plasma cell myeloma; from the spleen to the endocrine system in the two acute leukemias and from the spleen or from the liver in the two chronic leukemias.

When the lungs are compared to the endocrine system, it appears that the metastatic direction may be reversed. This remark is particularly true for the plasma cell myeloma.

Generally speaking, the association between the spleen and endocrine system metastases did not increase in presence of lungs metastases (Table 5).

Table 3 shows that the metastatic path to the central nervous system originates in the spleen, with the exception of the plasma cell myeloma, where metastases can originate either in the liver or in the spleen.

For the four types of leukemias, the spleen seems to be the organ which diffuses metastases to the central nervous system. The sign test can be significant either with or without metastases in the liver or only when the liver is also seeded. In chronic lymphocytic leukemia and acute myeloblastic leukemia, it seems that the metastatic spread originates always in the spleen, and that the liver is sometimes included in the metastatic spread (Table 3 and 5). However, either the association is higher in the absence of liver metastases or such association does not increase in presence of liver metastases. The lungs are not involved in the seeding of the brain. Such conclusion is obtained by looking at the bottom of Table 3 and 5. The spleen is related to the seeding of the central nervous system in presence and absence of lungs metastases. However, the association between the spleen and brain metastases is not increased in presence of lungs metastases.

These individual results can be summarized by the cascade sequence shown in Fig. 1.

The lymphatic system was also examined in its relationship to the plasma cell myeloma and the four types of leukemia. It appeared that only for acute myeloblastic leukemia a metastatic path could be established from the spleen to the four lymphatic areas.

Discussion

The cascade sequences that have been developed here for myeloma and leukemias are strikingly different from the corresponding sequences that have been found in corresponding studies of the solid tumors.

Whereas the generalization of the disease for the solid tumors characteristically involves metastases to the lungs as a key step in the cascade, the metastases to the spleen seems to be the key step in the cascade processes studied in this paper.

Elucidation of the cascade sequences in the processes of metastases does not in itself establish the detailed mechanism of the process. However, it is an important step in this direction, and it can provide some insight into the mechanism of metastasis even though it cannot reveal the fine details. For example, the marked

Table 3. Sets of 2×2 tables (presence or absence of metastases in paired organs with or without metastases at third site) by different type of histology. (Chi-squares applied to the off diagonal elements, i.e. presence of metastases only at one site)

Histology		Liver −		Chi-square	Liver +		Chi-square	Spleen −		Chi-square	Spleen +		Chi-square
		SPL −	SPL +[c]		SPL −	SPL +		LI −	LI +[e]		LI −	LI +	
Plasma cell myeloma	CNS −[a, d]	45	8	2.50	10	8	6.13*	45	10	4.08*	8	8	2.50
	CNS +[b]	2	2		0	2		2	0		2	2	
Acute lymphoblastic leukemia	CNS −	24	20	2.70	3	17	12.50*	24	3	2.77	20	17	0.03
	CNS +	10	19		1	34		10	1		19	34	
Chronic lymphocytic leukemia	CNS −	2	1	0.00	3	16	11.53*	2	3	1.33	1	16	14.06*
	CNS +	0	0		1	14		0	1		0	14	
Acute myeloblastic leukemia	CNS −	63	32	16.45*	1	44	34.04*	63	1	2.29	32	44	15.79*
	CNS +	6	13		3	48		6	3		13	48	
Chronic myelocytic leukemia	CNS −	8	7	3.13	3	21	19.45*	8	3	0.25	7	21	14.09*
	CNS +	1	2		0	7		1	0		2	7	

Histology		Lungs −		Chi-square	Lungs +		Chi-square	Spleen −		Chi-square	Spleen +		Chi-square
		SPL −	SPL +		SPL −	SPL +		LU −	LU +[f]		LU −	LU +	
Plasma cell myeloma	CNS −	54	15	8.47*	1	0		54	1	0.00	15	0	1.33
	CNS +	2	3		0	1		2	0		3	1	
Acute lymphoblastic leukemia	CNS −	21	14	4.50*	1	13	8.64*	21	1	0.80	14	13	0.30
	CNS +	4	17		1	16		4	1		17	16	
Chronic lymphocytic leukemia	CNS −	4	8	4.00*	1	9	7.11*	4	1	0.50	8	9	0.00
	CNS +	1	8		0	6		1	0		8	6	
Acute myeloblastic leukemia	CNS −	56	38	23.81*	1	25	15.75*	56	1	1.50	38	25	3.18
	CNS +	5	13		3	41		5	3		13	41	
Chronic myelocytic leukemia	CNS −	9	20	15.43*	2	8	6.13*	9	2	0.00	20	8	1.45
	CNS +	1	3		0	6		1	0		3	6	

* Chi-square significant at a probability level below 5% (sign test).

[a] − = Absence of metastases at specific site.

[b] + = Presence of metastases at specific site.

[c] SPL = Spleen.

[d] CNS = Central nervous system.

[e] LI = Liver.

[f] LU = Lungs.

Table 4. Sets of 2 × 2 tables (presence or absence of metastases in paired organs) by different type of histology. (Chi-squares applied to the off diagonal elements, i.e. presence of metastases only at one site)

Histology		Lung −	Lung +	Chi-square	Liver −	Liver +	Chi-square	Spleen −	Spleen +	Chi-square
Plasma cell myeloma	Kidney −[a]	66	1	4.90*	52	16	3.68	52	14	3.87*
	Kidney +[b]	9	2		6	5		5	6	
Acute lymphoblastic leukemia	Kidney −	34	6	7.26*	30	11	0.50	21	17	8.45*
	Kidney +	21	24		7	36		3	40	
Chronic lymphocytic leukemia	Kidney −	14	1	7.69*	4	10	8.10*	4	8	2.50
	Kidney +	12	21		0	33		2	23	
Acute myeloblastic leukemia	Kidney −	91	25	0.17	85	35	8.16*	61	53	33.75*
	Kidney +	29	50		14	65		7	67	
Chronic lymphocytic leukemia	Kidney −	34	5	2.12	18	19	7.04*	10	18	11.25*
	Kidney +	12	18		5	23		2	19	

Histology		Liver −		Chi-square	Liver +		Chi-square	Spleen −		Chi-square	Spleen +		Chi-square
		SPL −	SPL +[c]		SPL −	SPL +		LI −	LI +[d]		LI −	LI +	
Plasma cell myeloma	Kidney −	43	8	0.75	9	6	2.29	43	9	1.23	8	6	1.13
	Kidney +	4	2		1	4		4	1		2	4	
Acute lymphoblastic leukemia	Kidney −	20	8	2.50	1	9	4.90*	20	1	0.00	8	9	0.64
	Kidney +	2	5		1	35		2	1		5	35	
Chronic lymphocytic leukemia	Kidney −	2	1	0.00	2	7	1.78	2	2	0.50	1	7	5.14*
	Kidney +	0	0		2	23		0	2		0	23	
Acute myeloblastic leukemia	Kidney −	58	21	8.65*	3	32	27.27*	58	3	0.13	21	32	11.80*
	Kidney +	5	9		1	57		5	1		9	57	
Chronic myelocytic leukemia	Kidney −	8	6	2.29	2	12	7.69*	8	2	0.00	6	12	4.27*
	Kidney +	1	3		1	16		1	1		3	16	

* Chi-square significant at a probability level below 5% (sign test).

[a] − = Absence of metastases at specific site.

[b] + = Presence of metastases at specific site.

[c] SPL = Spleen.

[d] LI = Liver.

Table 5. Chi-squares obtained to test the strength of the association between metastases at two sites, with and without metastases at a third site

Type of 2 × 2 table	Endocrine vs. spleen		Endocrine vs. liver		Kidney vs. liver		Kidney vs. spleen	
Histology	LI −* chi-square	LI +* chi-square	SPL − chi-square	SPL + chi-square	SPL − chi-square	SPL + chi-square	LI − chi-square	LI + chi-square
Plasma cell	0.21	0.87	4.41*	0.31	0.21	0.23	0.25	1.06
Acute lymphoblastic	23.63*	2.33	0.03	0.05	0.31	6.24*	2.76	0.01
Chronic lymphocytic	—	0.05	0.09	0.14	0.09	0.31	—	0.28
Acute myeloblastic	25.66*	1.74	0.005	0.84	0.06	9.19*	6.10*	1.10
Chronic myelocytic	0.25	0.68	0.11	1.10	0.00	0.73	0.32	0.03

	Endocrine vs. spleen		Endocrine vs. lungs	
	LU − chi-square	LU + chi-square	SPL − chi-square	SPL + chi-square
Plasma cell	0.01	—	3.45	3.43
Acute lymphoblastic	5.71*	2.70	2.85	6.01*
Chronic lymphocytic	0.44	3.80	0.15	3.23
Acute myeloblastic	19.39*	0.07	2.50	4.32*
Chronic myelocytic	0.32	3.36	1.09	0.40

	CNS vs. Spleen[a]		CNS vs. Liver		CNS vs. Spleen		CNS vs. Lungs	
	LI − chi-square	LI + chi-square	SPL − chi-square	SPL + chi-square	LU− chi-square	LU + chi-square	SPL − chi-square	SPL + chi-square
Plasma cell	1.18	0.55	2.59	0.31	1.92	0.00	8.60*	0.53
Acute lymphoblastic	2.07	1.27	0.58	2.24	7.32	0.35	0.06	0.05
Chronic lymphocytic	—	0.08	0.15	0.009	0.44	0.07	3.84*	0.84
Acute myeloblastic	6.60*	1.98	9.85*	5.72*	4.94*	1.10	9.94*	14.09*
Chronic myelocytic	0.00	0.06	3.27	0.07	0.11	0.15	3.49	2.73

* Chi-square significant at 5% probability level.
[a] Central nervous system.
SPL = Spleen. LU = Lungs.
LI = Liver.

differences between the patterns of metastasis for the solid tumors and the patterns for myeloma and leukemias or the difference within the latter group can rule out some hypotheses about the metastatic process even though it is not possible to narrow the possibilities down to a single mechanism.

Consider, for instance, some of the possible hypotheses which the major role of the spleen in generalizing the disease would tend to confirm or disconfirm. The simplest hypothesis, that all of the diseases not grouped under the heading of "cancer" have the same mechanism of metastasis, can be decisively rejected. A related hypothesis, that they all have the same etiology, cannot be as decisively rejected but becomes dubious in view of the present findings.

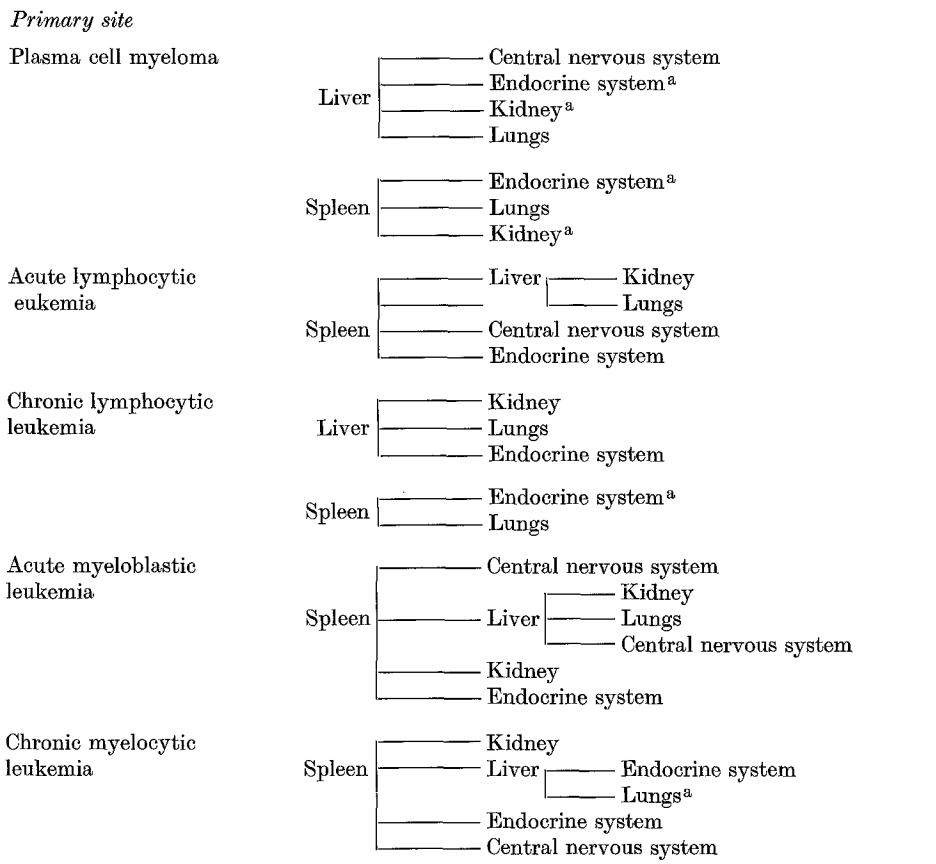

Fig. 1. Diagrams of the metastatic paths in the plasma cell myeloma and leukemias. [a] Suggested path (sign test not significant at the 5% probability level)

What hypotheses might be compatible with or account for the differences in the cascade processes between solid tumors and myeloma and leukemias ? Some such hypotheses would involve the differences between the respective normal cells which gave rise to the abnormal cells. Thus the solid tumors come from cells which have a relatively fixed environment, whereas the cells studied here would derive from normal cells which were relatively mobile or migratory. The normal behavior of the cells might explain some of the differences found here. With solid tumors, the lung parenchyma might be expected to act as a filter for metastatic cells but not for cells which would normally circulate in the hemopoietic system. This, however, would not explain why the spleen, which is also part of the hemopoietic system, is involved.

The dominant role of the spleen might be explained by various possible hypotheses, some likely for other reasons and some not. One simple hypothesis might be that the changes that result in a malignant cell originally occur in the spleen,

and that the sites which are considered here as the primaries are really metastases from the spleen. There may be other data that are incompatible with this hypothesis, but it cannot be ruled out with the data presented here. A somewhat less startling, but nevertheless related hypothesis would be that the myeloma and leukemias are multifocal, and the spleen is one of the first sites affected. Still less startling, but still related, would be the hypothesis that a multi-step transformation is required for metastases, and that the last step in transformation takes place in the spleen. Although all of these hypotheses are speculative, there are possible experiments which could confirm or disconfirm them. For instance, the multi-step transformation hypothesis would suggest looking for differences between the abnormal cells in the marrow and the abnormal cells in the spleen with respect to cell surface properties that would increase the chances of metastasis.

While the differences in the cascade sequences between the myeloma and leukemias considered here are less noticeable and therefore more difficult to establish statistically, there seems to be some differences in the patterns of metastases.

Whereas the spleen is the principal diffusing organ in all the four leukemias, the liver as well as the spleen appeared to be the main diffusing organ in the plasma cell myeloma and, sometimes, in the chronic myelocytic and lymphocytic leukemias.

Appendix

If the cascade hypothesis between two sites is likely, no or very few metastases should be present at one site, if metastases are not present at the other site. Therefore, the two off diagonal elements are the crucial values to establish a metastatic dissemination between two organs, as opposed to a random spread of metastases from the primary tumor throughout the body.

The general rules to establish a metastatic path in leukemias and myeloma are the following:

1. If only two metastatic organs are compared (Table 1), such as the spleen vs. the lungs, the metastatic trend is determined by the off diagonal elements, i.e. by the count of metastases present only at one site vs. the count of metastases present only at the other site. If the chi-square is significant at a 5% probability level, the null hypothesis (random spread of cancer from the primary tumor) is rejected. The alternative hypothesis is that a metastatic dissemination from one organ to the other can be established; for example, from the spleen to the lungs in the plasma cell myeloma and the four leukemias. No metastatic diffusion is detectable between the spleen and liver in the plasma cell myeloma (the off diagonal elements are equal).

2. When three sites are considered simultaneously, such as the endocrine system, liver and spleen, the path is suggested by the off diagonal values (Table 2). If the sign test is significant, the null hypothesis of a random spread of metastases is rejected as before (two sites only).

To understand the role of a third site in the spread of cancer, i.e. whether the third site should be included in the multistep spread of metastases, one should consider if the association of metastases at two sites increases when metastases are also present at a third site (Table 5).

Table 5 includes all the chi-squares which tested the strength of the association of metastases at two sites, with and without metastases at a third site.

Let us, for example, consider metastases in the spleen and endocrine system with and without liver metastases (acute myeloblastic leukemias). It appears (Table 2) that only one sign test is significant (suggested path = spleen vs. endocrine system in the presence of liver metastases).

To ascertain whether the liver has be be included in the metastatic dissemination, Table 5 has to be considered.

It appears that the highest association between metastases in the endocrine system and spleen occurs when metastases in the spleen are absent. Therefore, the suggested path is from the spleen to the endocrine system, without intermediate sites, such as the liver.

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