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
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 deter-
mined 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).