MEDICAL PRACTICE

Clinical Problems

Surgical Treatment of Pulmonary Metastases from Testicular Tumours

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Summary

Isolated pulmonary metastases from testicular tumours were treated by surgery in nine patients. Six are alive and well with no clinical evidence of recurrence. Three of the survivors were operated on more than 10 years ago. Surgical treatment should be considered in such patients, particularly as the metastases are often solitary and may be better differentiated histologically than the primary tumour. Mortality and morbidity rates after thoracotomy are minimal.

Introduction

It is often assumed that the development of a distant metastasis after the removal of a primary tumour is of particularly grave significance, being taken as a sign of widespread dissemination. This generalization may be true for some lesions but does not apply in the case of testicular tumours, where there is not only a significant incidence of truly solitary metastases¹ but long-term survival after their removal has been recorded on a number of occasions.

The surgery of lung metastases has progressed considerably since Gerulanos's report² in 1898 of the removal of part of a lung invaded by a chest-wall sarcoma in a 15-year-old boy. He later died, but the feasibility of such a procedure was

established. A recent report of pulmonary resections for tumours metastasizing from a wide variety of primary carcinomas and sarcomas recorded a gross one-year survival of 78% and a five-year survival of 33%.³ The first recorded removal of a testicular metastasis from the lung was in 1948,⁴ and sporadic reports followed.⁵⁻¹⁰

During the past 15 years at the Brompton and King's College Hospitals we have had under our care a number of patients with pulmonary metastases from testicular tumours. We describe the cases of these patients briefly and assess the results of surgical treatment.

Patients

Altogether nine patients (aged 19-58 years) with apparently solitary metastases from testicular teratomas were seen by us at the above hospitals between 1957 and 1968. All the primary tumours had been removed before the patients were referred to us, and in all cases radiotherapy to the abdomen and pelvis followed orchidectomy. Patients with pulmonary metastases from testicular seminomas are not included in this series. The radiosensitivity of this lesion is such that effective total thoracic irradiation can be accomplished and yet be within tolerance for pulmonary tissue.¹¹

A careful search was instituted for evidence of other metastases before recommending thoractomy, but undue delay was avoided. Initially it was felt that the extent of resection for intrathoracic secondaries should be similar to that employed in the treatment of primary bronchial carcinoma—that is, removal of a lung or lobe complete with its related lymph nodes. We now feel that the preservation of lung tissue is important, as local recurrence is unusual and resections for further metastases may be required at a later date.^{1 12} In the present series one patient had a segmental resection, seven had lobectomies, and one had two lobes removed in addition to block dissection of the mediastinal glands.

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Case Reports

Case 1.—Man aged 47. Eleven months after orchidectomy for an anaplastic teratoma of the left testis a routine chest radiograph showed a metastasis in the right lung. Therapy with actinomycin D and medroxyprogesterone was given for five months, but the tumour, which remained solitary, continued to grow slowly. He was referred for surgery, when a middle lobectomy (Fig. 1) was performed. Histologically the metastasis was well differentiated. He was alive and well two and a half years later.

FIG. 1—Right middle lobe removed in Case 1, showing the unusual occurrence of involvement of the bronchus by tumour.

Case 2.—Man aged 28. Two years after right orchidectomy for an anaplastic teratoma a routine chest radiograph (Fig. 2) showed a metastasis in the left lung. Left upper lobectomy was preceded by a four-day course of melphalan. The metastasis was well differentiated. Thirteen and a half years later he was alive and well, with no evidence of further recurrence.

FIG. 2—Well demarcated, rounded opacity in the left upper lobe in Case 2.

Case 3.—Man aged 19. Four years and three months after a left orchidectomy for an anaplastic teratoma routine chest radiography showed a metastasis in the left lower lobe. A left supraclavicular node was also palpable. The node was removed. It was involved by a cystic structure lined by columnar epithelium with smooth muscle in parts. This was taken to be maturation in a malignant teratoma. The pulmonary metastasis, which was removed by segmental resection, was histologically similar to the nodal metastasis. Twenty months later additional pulmonary metastases developed which responded partially to further chemotherapy after being unresponsive to actinomycin D alone. The patient then developed bony metastases and died two years eight months after thoracotomy.

Case 4.—Man aged 28. Eight months after a left orchidectomy for choriocarcinoma the patient developed left pleural pain. A chest radiograph showed a lower lobe mass; this was treated by lower lobectomy. Histologically the tumour was a choriocarcinoma invading the pulmonary veins. He developed generalized metastases and died 15 months later.

Case 5.—Man aged 38. One year after left orchidectomy for a teratoma a routine chest radiograph showed a metastasis. This was treated by right upper lobectomy (Fig. 3). Histologically the tumour consisted of undifferentiated tissue with groups of cuboidal and columnar epithelial cells which infiltrated surrounding tissue. He remained alive and well over 13 years after his thoracotomy.

FIG. 3—Right upper lobe removed in Case 5, showing typical subpleural site of metastasis, which measured 1.5 cm in diameter.

Case 6.—Man aged 39. Fourteen months after right orchidectomy for a teratoma, intermediate group B, this patient developed lethargy and lost weight. Chest radiography showed metastases in the right upper and middle lobes and at the hilum. A six-week course of radiotherapy to the mediastinum produced some regression, and thoracotomy was advised. A mass involving upper and middle lobes and paratracheal glands was removed, sacrificing the phrenic nerve. Histologically the tumour was extremely necrotic, with very few viable cells, compatible with metastatic teratoma. He remained free of further recurrence over 12 years later.

Case 7.—Man aged 32. One year after simple orchidectomy for a testicular teratoma in Ankara a routine chest radiograph showed two opacities in the right upper lobe and one in the right lower lobe. Following therapy with actinomycin D and testosterone the upper lobe shadows disappeared while the lower lobe shadow decreased in size. The latter, however, subsequently enlarged and

was removed by lower lobectomy, no evidence being found at operation of upper lobe metastases. The histological appearance of the tumour—which was cystic, lined by columnar mucus-secreting cells, with muscle, fibrous tissue, and lymphocytic infiltration—was that of a secondary teratoma which had undergone a remarkable degree of differentiation.

Case 8.—Man aged 58. This patient underwent right orchidectomy for an undifferentiated teratoma, though a chest radiograph showed a left upper lobe opacity for which treatment was not given. Two years later an opacity appeared in the right lung; this disappeared spontaneously. The left lung shadow, which was enlarging, regressed after a course of radiotherapy. One year later left upper lobectomy was carried out for further enlargement, but he soon developed bony metastases and died. Histologically the pulmonary metastases showed the same degree of differentiation as the primary tumour.

Case 9.—Man aged 24. Nine months after right orchidectomy for a teratoma a routine chest radiograph showed a left lower lobe opacity. This was considered to be a metastasis and was treated with radiotherapy. Gradual enlargement, however, occurred, and seven months later the patient was referred for surgery, when a well-differentiated metastasis was removed by left lower lobectomy. Three months later he remained well.

Results

There were no deaths attributable to thoracotomy, and morbidity was minimal, most of the patients being discharged from hospital within two weeks of operation.

At the time of writing, six of the nine originally treated were alive and well, three for more than 10 years after thoracotomy. This group includes Case 6, in which 12 years previously two lobes were resected with massive hilar glands.

Three died of widespread metastases. In Case 4 the metastatic choriocarcinoma invaded the pulmonary veins, while in Case 8 the pulmonary metastasis was not treated for two years after discovery.

Discussion

Evaluating the role of surgery in the treatment of these metastatic tumours is difficult, particularly when this is a part of a combined radiotherapeutic and chemotherapeutic approach. A further problem is caused by the possibility of maturation of the tumour, with histological regression and conversion into a benign residuum.^{13 14}

Radiotherapy was employed before surgery in three instances in this series. Histologically the mediastinal glands in Case 6 were mainly necrotic tissue, though some cells were considered viable. Regression occurred after a short course of radiotherapy in Case 8; however, this was soon followed by further enlargement. It is possible that only parts of the tumour are radio-sensitive. Decrease in size after radiotherapy may follow necrosis of radiosensitive cells, while further enlargement is due to growth of more radioresistant tissue. The experience of others fails to clarify the problem completely. Five out of seven patients with pulmonary metastases from testicular tumours were treated solely by radiotherapy. Three patients died after a short interval. Two, however, were alive at 52 and 171 months. Two others treated by surgery alone were alive at 107 and 128 months.¹⁵

Similar problems are associated with interpreting results after chemotherapy (Cases 1, 2, and 7). In Cases 1 and 2, where tumours were highly differentiated, treatment produced no evidence of regression. In Case 7, however, two lung shadows presumed to be secondaries disappeared after treatment with actinomycin D, while the histological features of a metastasis which was removed were unusual, possibly due to the destruction of part of the tumour. Alternatively, spontaneous regression may have occurred. The disappearance on radiographs of pulmonary metastases has been attributed to complete change into a benign residuum or to clearing of inflammatory

reaction surrounding a metastatic embolus. The latter may later grow to a detectable size and again become visible.¹⁶

The importance of frequent chest radiographs in the follow-up of patients with testicular tumours treated by orchidectomy has been emphasized,¹⁵ while the value of a radiograph at the first evaluation is evident. Six out of nine patients in this series were asymptomatic when routine radiographs showed pulmonary metastases. It would seem sensible to advise three-monthly chest radiography at least for a few years after orchidectomy, particularly as in this series the mean interval between orchidectomy and detection of metastases was about one year. Tomography was carried out in all the present cases, but in our experience it has rarely added to information provided by good quality plain radiographs.

Evidence of multiple metastases or mediastinal node involvement is a bad prognostic sign;¹⁷ nevertheless, radiotherapy may render the latter operable, as Case 6 clearly illustrates. Lymphography to show occult metastases in the pelvic, abdominal, and mediastinal lymph nodes has, we feel, an important role.

The commonest site for secondary tumours is the subpleural position¹⁸ (Fig. 3), though they occasionally occupy a more central position and may rarely invade a bronchus (Fig. 1). This may account for our observation that cytological examination of sputum was of little diagnostic value, which is at variance with other reports.¹⁹

The timing of surgical intervention is controversial. Asvall *et al.*¹⁵ recommend operation as soon as pulmonary metastases are diagnosed provided there is no evidence of further secondaries. Others¹⁸ advise a few months' observation to ensure so far as possible the absence of widespread dissemination. In general we tended towards the latter view, though undue delay in recommending surgery was considered to be unjustifiable.

Metastases from testicular tumours may have unusual growth and invasive characteristics.^{6 14 17} Histologically the metastases may show higher differentiation than the primary tumours (Cases 1, 3, and 7). The secondary tumour in Case 8 was as undifferentiated as the primary one. This may be related to the patient's unfavourable clinical course. It is probable that the long-term survival of some of the patients in the present series was related to the slowness of the tumour growth, which correlates well with a good prognosis, as was reported by Spratt and Yuen.²⁰ Nevertheless, they produced evidence based on tumour growth curves which indicated that survival was further prolonged by surgical treatment.

The duration of the interval between removal of the primary tumour and the discovery of metastases has been said to be related to the prognosis.^{21 22} In other reports this view is disputed.²³⁻²⁵ In our short series this factor is impossible to evaluate, though it is noted that the patient who had pulmonary metastases at the time of orchidectomy (Case 8) died, as did the patient whose metastases were detected 51 months after orchidectomy (Case 3).

Blandy,²⁶ in a review of the treatment of testicular tumours, made no reference to the surgical treatment of pulmonary secondaries, while earlier reports indicated that the prognosis of such patients was very poor.⁵ Our experience, however, indicates that surgery may have much to offer in selected cases, whether on its own or in a supportive role to other forms of treatment.

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Standardization of the One-stage Prothrombin Time Test for the Control of Anticoagulant Therapy: Availability and Use of Thromboplastin Reference Preparations

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Introduction

Prothrombin time determinations are used for the control of anticoagulant therapy with coumarin drugs. The results obtained at different centres at present give different assessments of the abnormality because the thromboplastin preparations do not have the same sensitivity to the coumarin defect. There now seems to be general agreement that the thromboplastin sensitivity ratio method of Biggs and Denson¹ using characterized thromboplastin preparations can be used to correlate the prothrombin time results obtained at different laboratories. Another approach to the standardization problem has proposed the use of standard reference plasma samples.² This is still under investigation, since possibly characterized thromboplastin preparations will be used together with reference plasma preparations to give a complementary system. At present the plasma standards have not been studied with a wide range of thromboplastin preparations at the Laboratory of Biological Standards. It is, however, already possible to use the characterized thromboplastin preparations with individual fresh normal and abnormal samples from patients stabilized on anticoagulant therapy. This communication concerns the availability and use of the thromboplastin reference preparations.

Preparations

At present five preparations of thromboplastin are available from the Division of Biological Standards. Two (2 and 3 below) have been characterized and can now be issued for standardization procedures. The other three are under study and will be available shortly for general use.

Thromboplastin 1 (69/223): human brain, plain, to be reconstituted with 1 ml distilled water.

Thromboplastin 2 (67/40): human brain with fibrinogen and factor V, to be reconstituted with 2.2 ml 3.2 mmol CaCl₂.

Thromboplastin 3 (68/434): bovine brain with fibrinogen and factor V, to be reconstituted with 2.2 ml 3.2 mmol CaCl₂.

Thromboplastin 4 (70/115): rabbit brain with fibrinogen and factor V, to be reconstituted with 2.2 ml distilled water.

Thromboplastin 5 (70/178): rabbit brain, plain, to be reconstituted with 1 ml distilled water.

This range of thromboplastin reference preparations has been provided to take into consideration the various modifications of the one-stage prothrombin time in use in different parts of the world. All these types of thromboplastin preparations have been sealed in ampoules under conditions which should ensure their long-term stability as reference materials.

A collaborative study carried out in Leiden, Oslo, and Oxford in 1969³ showed that the three laboratories agreed closely when they tested preparations 2 (67/40) and 3 (68/434) on coded common abnormal plasmas. In all laboratories the same clotting time ratio was obtained for each of these coded plasmas. The same relative sensitivity ratio for both thromboplastins was obtained in all laboratories, both with common abnormal plasmas and with the local abnormal plasma used in the three laboratories. This shows that thromboplastin preparation 2 (67/40) can be used as a reference preparation to calibrate bovine thromboplastin preparations with respect to the coumarin defect. Additional work suggests that the human brain preparation 1 (69/223) can also be similarly calibrated. A collaborative study is in progress to confirm the results for the human brain preparation 1 (69/223) and to calibrate the rabbit brain preparations (4 and 5) (70/115 and 70/178) in terms of preparation 2 (67/40).

Meanwhile we feel that ampoules of the two types of thromboplastin preparations already studied (2 and 3) (67/40 and 68/434) should be made available for use. A sensitivity ratio of 2.0 can be assigned by definition to preparation 2 (67/40). The collaborative study showed that thromboplastin bovine preparation 3 (68/434) was determined as having a ratio of about 2.0 in terms of 67/40. Other thromboplastin preparations can be calibrated in terms of preparation 2 (67/40). Memoranda of information about each reference preparation will be issued with ampoules, together with instructions on how to calibrate and apply the sensitivity ratio prepared by Denson.⁴

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