
Complete spontaneous regression of cancer: Four case reports, review of literature, and discussion of possible mechanisms involved

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Abstract

Spontaneous regression or remission (SR) of cancers has been defined as the disappearance of the malignancies without any treatment or with obviously inadequate treatment. Four case reports are presented. These include a case of pleomorphic liposarcoma with bilateral lung metastases, a case of recurrent squamous cell carcinoma of the esophagus following esophagectomy a year earlier, a case of a squamous cell carcinoma of the scalp, and a case of a ruptured hepatocellular carcinoma with an emergency right hepatic lobectomy but with some gross cancer remaining in the left hepatic lobe.

The literature of SR of cancers was reviewed and various mechanisms possibly involved in the disappearance of the cancers were discussed. Although immune modulation has been stated to be the most likely process causing SR, other mechanisms, such as genetic therapy, withdrawal of carcinogens, infection, fever and vaccine roles, apoptosis, antibody, antiangiogenesis and maturation mechanisms, withdrawal of therapy, natural killer activity, endocrine, hormonal, and pregnancy factors, and prayers or psychoneuro-religious participation were also mentioned. Induction and inhibition of malignant protein expression and repair of gene damage may prove to be the more important processes in cancer regression.

It was also pointed out that the pulmonary metastases of the liposarcoma and the recurrent squamous cell carcinoma of the esophagus may be the very first cases of their kind to be described and that it is rare indeed to find 4 cases of SR's in a solo practice.

Finally, it is likely that SR is rarer than previously believed and that the incidence may be one in every 140,000 cases of cancer rather than the one per 60,000 to 100,000 cancer cases as earlier thought.

Introduction

Spontaneous regression or remission (SR) of cancers has been defined by Everson and Cole¹ as the complete or partial, permanent or temporary disappearance of all or at least a significant portion of a well diagnosed malignant tumor in the absence of all treatment or in the presence of therapy which is considered inadequate to exert a significant influence on the neoplastic disease. Remissions are supposed to last at least one month and should not just be the waxing and waning of stable disease. This definition of SR is considered unequivocal for cancer regression with no medical therapy, treatment failure, or therapy known to be failures.

The true incidence of SR is unknown, but Cole² has estimated that probably it occurs in no more than once in 60,000 to 100,000 people with cancer. After a review of a large number of cases, Cole was able to document only 176 cases from 1900-1964. Lymphomas and leukemias were not counted. Therefore, if one SR occurs, on an average, in about 80,000 persons with cancer, it would require a single surgeon working about 30 years and seeing about 10,000 cases of cancer a year, before he would find 4 spontaneous regressions. But if only one SR occurs in 140,000 cancerous cases, a surgeon would need to see nearly 19,000 cases of cancer a year for 30 years, or a total of 570,000 cancer cases, before he would find 4 cases of SR.

Nearly two thirds to three fourths of all SR's occurred in just a few types of cancers. Furthermore, most soft tissue sarcomas occurred earlier this past century and have been difficult to find in recent literature. Even with the extensive review by Everson and Cole,¹ only eleven cases of soft tissue sarcomas with SR were recorded. None were pleomorphic or dedifferentiated liposarcomas.

After a current check of more than 1200 citations and references in a literature search, it was hard to find any cases of regression of metastatic pleomorphic liposarcoma to the lungs and of recurrent squamous cell carcinoma of the esophagus. There was a case of spontaneous remission of lung metastases from an esophageal primary but the primary esophageal lesion did not regress except only partially.¹⁰⁰ Furthermore, SR also seemed to occur much less frequently than previously thought and was found to occur at a rate of 1 per 140,000 cases of cancer.

Because of the extreme rarity of finding 4 cases of SR in a solo practice of a surgeon and because the patients with metastatic pleomorphic liposarcoma and recurrent esophageal squamous cell carcinoma may be the first cases of their kind to be reported, this paper is being presented with the 4 case reports, review of the literature, and a discussion of possible mechanisms involved in SR.

First Case Report

Mrs. A. T., 69-year-old part-Hawaiian and part-Caucasian woman, noted a 3.0 cm rounded, tender mass in the left gluteal area after a fall in late 1996. X-rays and sonograms showed a homogeneous soft tissue density, 5.0 x 5.2 cm, with well-defined margins in the left gluteal region suggestive of a hematoma. The lesion slowly increased in size and, therefore, surgical consultation was sought in December 1997. Except for the left gluteal mass, her physical examination was unremarkable.

MRI study of the left gluteal region showed an 8.0 cm soft tissue

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mass involving the fat overlying the left gluteus maximus muscle without definite invasion of muscle. Excision biopsy of the lump was done on 01/09/98. With the exception of transient atrial fibrillation, she did well. The histological examination of the 12.0 cm x 7.0 cm lesion showed a high-grade pleomorphic liposarcoma. A surgical margin was focally involved. Subsequently, wide radical re-excision, including portions of the left gluteus maximus muscle, was carried out. Pathology examination revealed no evidence of residual sarcoma. She was seen in consultation by a medical oncologist and a radiation therapist. The latter subsequently delivered 6,480 rads to the left gluteal area.

Because of some necrosis involving the edges of incision, these areas were excised on 01/24/98. During the course of her therapy, studies revealed a lower left neck mass which required a left thyroid lobectomy on 02/25/98. Pathological examination noted an occult papillary carcinoma, 0.1 cm in greatest microscopic dimension without capsular or surgical margin involvement, associated with a multinodular goiter.

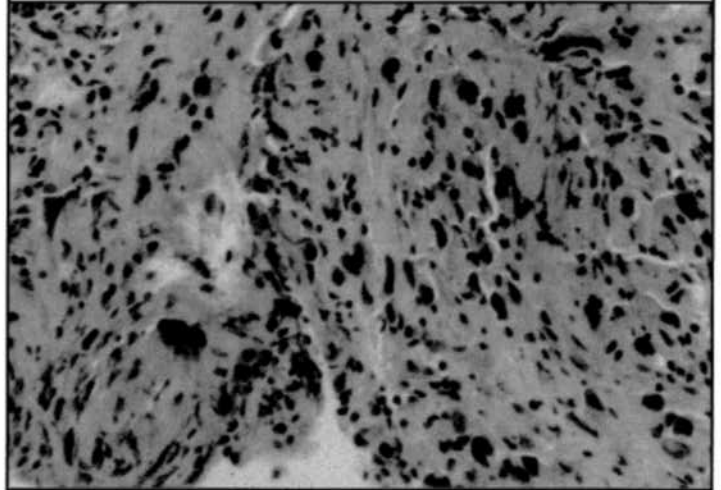
On 03/03/98, a large left hip seroma was drained by the insertion of two Jackson-Pratt drains. After the drains became plugged, the seroma reaccumulated, requiring frequent aspirations-drainage. Because of the persistent recurrence of the seroma, 250 mg of Doxycycline liquid was injected into the cavity in an attempt to sclerose the area and allow adherence of the walls of the cavity. But this caused the injection site to become necrotic and an area 1.0 cm in size to blackened. An eschar developed at the site. Furthermore, the seroma persisted.

On 09/03/98, chest x-ray showed a 3.0 cm mass in the anterior segment of the upper lobe of the right lung, a 1.0 cm mass in the lower lobe of the left lung, and a 3.0 to 4.0 cm mass in the left hilum (Fig 1a). CT scan of the chest, on 09/10/98, confirmed the presence of these masses.

Figure 1a. Chest x-ray shows metastases to lungs.



Figure 2a. Slide shows pleomorphic liposarcoma from biopsy of left hilar metastasis.



MRI studies of the left gluteal region on 09/16/98 showed only post-operative changes of the subcutaneous tissue. There was an encapsulated fluid collection or seroma in the operative site.

On 09/17/98, a CT guided needle biopsy of the left hilar mass was done. Pathological studies revealed malignant neoplasm, consistent with metastasis from the previously resected high-grade sarcoma of the left gluteal area (Fig 2a).

Before any new therapy could be given for the metastases to the lungs, another chest x-ray on 10/02/98 showed a decrease in the size of the pulmonary and left hilar metastases. Subsequent chest x-rays on 11/02/98 and 12/02/98 showed further regression of the lung and the hilar metastases. A CT scan of the chest on 05/14/99 and a chest

Figure 1b. Chest x-ray shows complete regression of metastases.



x-ray on 05/23/99 (Fig 1b) and on 08/02/99 revealed complete regression of all the metastases with no treatment at all.

On 08/11/99, excision of the left hip irradiated tissues, the eschar or necrotic injection site, and the pseudocapsule of the serous cavity were excised. Advancement of skin flaps were done for closure. Chest x-rays on 08/07/00 continued to show no evidence of metastases.

Comment

The evidence for spontaneous regression in this case is convincing. Histologically proven lung metastases disappeared with no therapy at all.

Second Case Report

Mr. M. S., a 57 year old Japanese man, had a near total gastrectomy, omentectomy, splenectomy, resection of the distal one third of the pancreas, jejunojejunostomy, and a feeding jejunostomy on 02/11/83 for a moderately well differentiated adenocarcinoma of the stomach superficially invading the underlying muscular layer. On 03/03/83, he had drainage of a left subphrenic abscess. Subsequently, he did well.

On 05/09/89, on a routine follow-up esophagogastroduodenoscopy, a 3.0 cm reddened area in the lower esophagus, 2.0 to 3.0 cm above the esophagogastric junction, was biopsied. The pathology report was squamous cell carcinoma of the lower esophagus. On 05/15/89, the patient underwent a resection of his gastric remnant and the distal third of his esophagus. An end-to-side esophagojejunostomy, side to side jejunojejunostomy and a feeding tube jejunostomy were also done.

Post-operatively, on 05/25/89, a gastrograffin swallow showed a leak of the esophagojejunostomy site with communication to the left pleura space. On the same day, a tube was placed in the left chest to drain the empyema. During the placement of the chest tube, the patient aspirated some gastric contents and developed pneumonia. On 06/07/89, a tracheostomy was done. The chest tube was discontinued subsequently when the patient recovered. The final pathology report showed moderately well differentiated squamous cell carcinoma of the distal esophagus invading the submucosa but not

involving the muscularis.

On 05/24/90, a year later, endoscopic biopsy of a 1.0 cm lesion at the esophagojejunal junction revealed recurrent squamous cell carcinoma. Five pathologists in three different hospitals in Honolulu, Hawaii, concurred that the patient had recurrent squamous cell carcinoma (Fig 2b). Consultants recommended further resection or radiation of the carcinomatous area. However, before any further therapy could be started, another endoscopy with biopsy done on 05/31/90 showed only severe inflammation. Repeated endoscopic biopsies done yearly from 1990 until 1998 did not reveal any recurrent squamous cell carcinoma. His last endoscopy and biopsy on 09/07/99 also showed no recurrent carcinoma and only a mild chronic inflammation of the esophagojejunal junction. He has remained free from his recurrent carcinoma without any treatment for at least 9 years.

Comment

Endoscopic biopsies were done a week apart in this case. The 05/24/90 biopsy showed recurrent squamous cell carcinoma while the 05/31/90 biopsy showed only inflammation. When subsequent endoscopies and biopsies showed no cancer, the original slides were reviewed and re-reviewed by three different pathologists at St. Francis hospital, by a Dr. H.N., from Queen's Hospital who wrote a formal consultation confirming the recurrent cancer, and by a Dr. G.S. from Kuakini Hospital at a presentation during a tumor conference. All agreed that there was recurrent squamous cell carcinoma of the esophagus.

While regression in squamous cell carcinoma in the esophagus is unusual and this may be the first reported case of SR in a recurrent esophagus cancer, remission in a week would be rare, but there have been other cases of other cancers that have regressed rapidly. SR is, after all, a remarkable phenomenon. Why it should even occur is certainly unknown.

Third Case Report

Mrs. M. K., an 87-year-old Chinese woman was seen on 08/11/95 because of two large necrotic lesions on her forehead and scalp. The one on the forehead was ulcerated, 2.0 x 4.0 cm in diameter, and

Figure 2b. Slide shows recurrent squamous cell carcinoma of the esophagus.

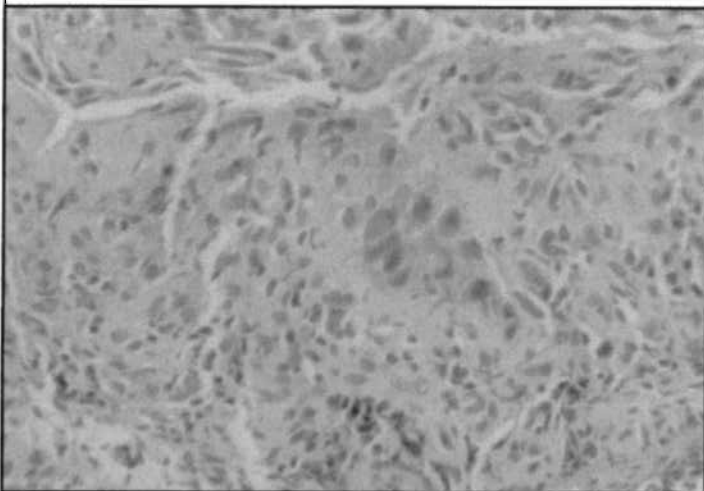
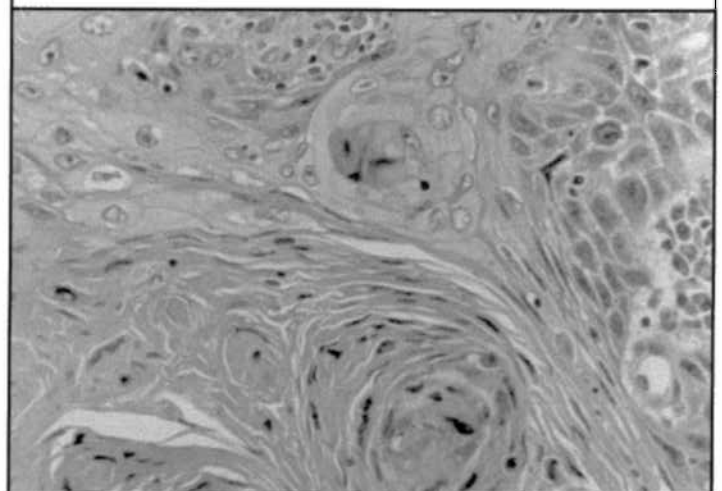


Figure 2c. Slide shows squamous cell carcinoma of the scalp.



umbilicated. On the vertex of the scalp was another similar 6.0 x 8.0 cm lesion that seemed infected. Past medical history revealed hypertension, end-stage renal disease, left ventricular hypertrophy, congestive heart failure, previous staphylococcus sepsis, gastric ulcers, altered mental status, pancytopenia, and multiple thrombectomies of clotted Gore Tex grafts required for hemodialysis.

On 09/08/95, an excision of the 4.0-cm ulcerated lesion on the forehead was done. Undermining of the scalp with a rotation flap graft was performed to close the defect. Biopsies of the larger 8.0 cm lesion on the vertex of her scalp were taken. Both areas were diagnosed as squamous cell carcinomas of the scalp (Fig. 2c). She was seen by a radiotherapist for treatment of the larger squamous cell carcinoma involving the vertex of the scalp. However, because the patient was uncooperative, no radiation or further treatment was initiated.

On 01/29/96, about 5 months later, the scalp lesion started to disappear. The areas that were once ulcerated, necrotic, and crusted now seemed smoother although somewhat reddened. By early May 1996, the squamous cell lesions of the scalp had completely and spontaneously regressed without any treatment. The scalp now looked normal without any redness. She remained free of cancer without any treatment until 12/14/98, when at age 91 years, she expired from staphylococcus aureus sepsis.

Comment

Although no repeat biopsy was done during the three years of remission, the scalp of this patient, from early May, 1996, was completely normal to physical examination and to all observers. It would have been excessive to have done a biopsy to prove that the normal skin was normal. Besides, the family was reluctant to even bring the patient to the office for follow-up as there no longer was any abnormality on her scalp. It would have been very difficult to justify another biopsy since even an office visit was considered unnecessary by her family.

Fourth Case Study

Mr. J. C., a 53 year old Chinese man from Tahiti, was seen on 04/14/70 because of an enlarging mass in his right upper abdomen. Examination, at that time, suggested a hepatocellular carcinoma. His past medical history revealed a Billroth II gastrectomy for a large benign gastric ulcer and cirrhosis of the liver in August of 1966.

Just prior to his scheduled laparotomy, he became hypotensive and was rushed into surgery. A large ruptured hepatocellular carcinoma in the right lobe of his cirrhotic liver was uncovered. Hemoperitoneum was evident. The cancer extended into the medial segment of the left lobe of the liver. Because of the emergency nature of the operation, the hypotension, and the cirrhosis of the liver, only a rapid right hepatic lobectomy was done. Gross cancer was left in the left lobe of the liver. Recovery was fortunately rapid and the patient was discharged on 04/21/70, 7 days after surgery.

Subsequently, he was given 5-fluorouracil weekly for a month but, because the patient wanted to return to Tahiti, further chemotherapy was not given. He, however, survived for 21 years more without any known definitive therapy. The patient was last examined in May 1987, in Honolulu, at which time, he was found free of cancer. He survived 21 years and died on 02/02/91 in Tahiti with no

evidence of recurrence of his hepatocellular carcinoma. The cause of his death was stated to be a stroke.

Comment

The pathological examination revealed the right lobe of the liver with a large ruptured hepatocellular carcinoma. The cancer had extended to and had involved the resected margin. Gross cancer was noted at the margins of resection on the specimen and on histological examination. At surgery, the cancer had invaded the left lobe of the liver. There were also nodules of cancer present in the left liver. Though cancer was left in the margin and elsewhere in the left lobe of the liver, this patient survived 21 more years without further treatment.

Review of literature and discussion of possible mechanisms involved in spontaneous regression of cancer.

Incidence

In a recent literature search for reports of complete spontaneous regressions of cancer, more than 1200 citations and references were secured. These involved papers from the 1970's until the present. In addition, a large number of articles and books published before 1970 were also reviewed. The largest number of references involved instances of SR in leukemias^{4,5,6,7,8,9} and lymphomas.^{10,11,12,13,14,15}

Because of the inconsistency and variability of the SR's in the leukemias and lymphomas,^{2,13} Everson and Cole¹ chose not to include them in their description of the 176 cases of SR found between 1900 and 1964. Why leukemias and lymphomas display this inconsistent and variable behavior is unknown. Why they should form such a relatively large group so as to consist of more than 50% of the reports of SR is also unknown.

Besides the 176 cases found between 1900 and 1964 by Everson and Cole,¹ another 188 cases of SR found between 1966 and 1985 were reported by Baker.⁸⁴ However, Challis and Stam⁶⁹ indicated that, between 1966 and 1987, there were 504 cases of SR. They included lymphomas and leukemias in their total.

A search of the literature for SR's of cancer between 1986 and 2000 revealed another 139 new cases. Partial regressions or cases not well documented or histologically proven were not included. Lymphomas, leukemias, renal cell carcinomas, and melanomas again formed the majority or 67.6%. There were 43 cases of renal cell carcinoma and 18 cases of melanoma.

If these 139 cases were added to the 176 cases of Everson and Cole found between 1900 and 1964 and the 188 cases of Baker, found between 1966 and 1985, there would be a total of 503 cases of SR last century. But if the 504 cases of Challis and Stam were to be added to the 176 cases of Everson and Cole and to the 139 new cases, there would be 819 of SR's of cancers during the past century instead.

Parkin⁹⁴ has stated that the estimate of new cancer cases for the year 1990 for every country in the world was 8.1 million. This number, however, excluded non-melanoma skin cancers. One half of the total cancers occurred in developing countries.

During 1994, 1,208,000 new cases of cancer were diagnosed in the United States.⁹⁵ In the mid 1990's hepatocellular carcinoma, probably the most common cancer in the world was estimated to be

over 1,000,000 cases yearly, and all cancer in the United States generally to be about 1,350,000 cases.⁹⁶ In Grunlee's article,¹⁰¹ there was a forecast made of the number of cancer cases expected to be diagnosed in the US in the year 2000. This number was 1,220,100. Most will be lymphomas (62,300 cases) and leukemias (30,800 cases). Esophageal carcinomas will constitute 12,300 cases and soft tissue malignancies 8,100.

Roughly, the number of cancer cases in the U.S. would be 19,500,000 in the period between 1985 and 2000. This would make an estimate of about 1 case of SR for every 140,000 cases of cancer, making the number of SR's in the U.S. even rarer than originally believed by Everson and Cole² who wrote that SR's occurred 1 in 60,000 to 100,000 cancer cases or by Baker⁸⁴ who thought that SR probably occurred more frequently.

The next 3 cancers with frequent numbers of SR's have been renal cell carcinomas,^{1,16,17,18} neuroblastomas,^{19,20,21,36} and malignant melanomas.^{1,22,23,24,28} They form the largest group of solid cancers known to have spontaneous regressions. Of the solid tumors, renal cell carcinomas seem to behave like leukemias with their regressions and recurrences.^{16,17}

Other solid cancers with anecdotes of spontaneous regression have also been described. Although of quite rare occurrences, lung cancers,^{1,27,28,32,79,80} epidermoid cancer of the bronchus,⁷⁸ hepatocellular carcinomas,^{1,25,26,32} choriocarcinomas³⁷ bladder malignancies,³⁵ soft tissue and bony sarcomas,¹ prostate cancer,³² colon and rectal cancers,^{1,32} malignancies of the ovary,³² breast,^{32,34} testis,³⁹ uterus,¹ bladder,^{32,34,37} stomach,^{3,29,32} larynx,^{1,32} thyroid,^{1,21} tongue,¹ pancreas,¹ and esophagus,^{33,100} have been described with SR's.

By comparison with the leukemias and lymphomas, the solid tumors have indeed been few and mention in recent literature of these solid cancers have been sparse. Is there a factor or factors that allow leukemias and lymphomas to spontaneously regress so much more frequently than, say, pleomorphic liposarcomas, or esophageal squamous cell carcinomas?

Possible mechanisms involved in spontaneous remission

Documented reports of complete spontaneous remissions of cancers are unusual, if not remarkable. Generally, regressions of cancers have tended to occur in lymphomas, leukemias, kidney cancers, neuroblastomas, and melanomas. There have been suggestions of "natural killing activity" in lymphomatous patients with regressions,⁵¹ and viral or bacterial infections causing enhancement of immune systems.^{88,89,90} Cytokine release and cellular immune activation causing apoptosis, differentiation of malignant tumors into benign ones, angiogenesis inhibition, genetic factors, and telomerase inhibition all have been mentioned as possible mechanisms in promoting spontaneous remissions.^{23,60,93,102}

Factors that may cause or be associated with SR have been listed elsewhere also.^{1,2,14,27,30,31,32,37,38} These involve modulations, modifications, manipulations or stimulations of the immune system^{2,19,23,30,31,37,38,43,50,52,60} with the use of various substances as vaccines,^{6,31,40,49,52} toxins,³¹ interleukins and interferons.^{3,44,45,46,63,64} In addition, transfusions,^{5,67} enzymes,⁴² gene therapy,⁹³ fever and infections,^{5,14,15,30,42} trauma or operations,⁶⁷ endocrines or hormones or pregnancy influences,^{47,53,51,81} elimination of carcinomas or irritants^{67,81} maturation or differentiation,^{48,81} cytotoxic or natural killer

cells with lytic activity against tumor cells lines,^{18,19,51,54,72} withdrawal of therapy,^{55,56} psychoneuro-spiritual immunologic factors,^{31,32,67,68,69,70,71} and angiogenesis therapy⁶⁶ have all been cited as playing roles in the regression of cancer.

Cytokines,^{3,59,60,81} especially interleukin, appear to play an important part in tumor regression causing necrosis and apoptosis.^{57,65} The latter effect can also be induced by cysteine proteases,⁵⁸ thus leading to spontaneous tumor regression in rat histiocytomas.

Immunological mechanisms:

Interleukin has been used effectively to inhibit cancer growth.^{3,85} SR is thought to be the result of an efficient immune response against melanoma cells in vivo critically influenced by a complex network of interacting cytokines present.^{57,83} Viral infections inducing host production of interferon with inhibition of tumor by interferon have been thought to be mechanisms for SR.⁸ The normalization of OKT4/OKT8 ratio may be a factor in cancer regression as suggested by Ribera⁸ and Hansen⁴⁹.

Chromosomal or genetic mechanisms:

Chromosomal or genetic abnormalities^{5,6,9,10,13,14,74,75,76,81} have been evident in cancer for some time. There has been also some information indicating that chromosomal manipulation such as deletion and enzymatic blockage⁷⁴ can cause remission.

DNA damaged by radiation or tobacco smoke can result in mutations commonly found in human cancers, such as lung carcinomas. Spontaneous oxidation of guanine residues in DNA generates 8-oxoguanine (oxoG). By mispairing with adenine during replication, oxoG gives rise to a G-C to T-A transversion, a frequent somatic mutation in human cancers.

A mending enzyme called 8-oxoguanine DNA glycosylase (hOGG1) can repair the damaged DNA by catalyzing the expulsion of damaged DNA. This is accomplished by cleavage of the DNA, thus cutting away the problem part (oxoG) with chemical reactions. What is cut out is a single letter of the genetic code, one of some 3 billion letters arranged in pairs to form an estimated 100,000 genes in humans.

The protein (hOGG1), a natural antioxidant, has been noted to pocket the damaged letter known as 8-oxoguanine (oxoG) which had resulted from free radical oxidation caused by carcinogens and to repair the damage to the DNA.

What is also interesting is the observation that partial or complete loss of hOGG1 has been linked in 60-70% of all lung malignancies. In these latter cancers, one of the genes for making hOGG1 has been deleted and, in small cell carcinoma which has a dismal prognosis, there was a complete loss of hOGG1.⁸³

Genetic enzymatic inhibition

Recent preliminary data¹⁰² have indicated that an Abl tyrosine kinase inhibitor has significant activity in chronic myelogenous leukemia (CML) even in those patients that interferon therapy has not helped. The consequence of the translocation of 2 genes, resulting in the Philadelphia chromosome, is the creation of a fusion protein Bcr-Abl which directs the production of activated tyrosine kinase. The latter promotes the chaotic proliferation of white blood cells in the bone marrow.

A designed agent, labelled STI 571, has been used to inhibit the

Abl kinase in CML and has had quite impressive complete hematologic responses in Phase 1 studies.

Gene switching

One of the more recent, interesting researches involving regressions of cancers has involved the "switching off and on of cancer" in mice. By putting the antibiotic tetracycline in the drinking water of leukemia stricken mice, even advanced stages of the leukemia disappeared. But when the antibiotic-spiked water was withdrawn, the cancer returned.

The mechanisms apparently involved the 2 genes, Bcr and Abl. Fusion would occur in a process called chromosomal translocation whereby the 2 genes fused when they were out of their normal positions on chromosomes. Inside a cell, the fused genes Bcr-Abl would direct production of tyrosine kinase. This enzyme would promote a chaotic proliferation of white blood cells in the bone marrow thus resulting in leukemia.

Given the tetracycline, these mice would switch off the gene and its leukemia-producing activity. Cancer cells then would stop reproducing and would begin to die. Cancer reversal in some animals have been induced as much as three times.

Tetracycline in mice and tyrosine kinase inhibiting drugs in humans can inhibit leukemia generation but they do not eliminate the fused Bcr-Abl. If resistance to the inhibitor develops, either species will relapse with leukemia.⁹³

New Approaches

New approaches which attack the molecular mechanisms by which the tumor gets its blood supply and hence its growth factors and oxygenation have been described.¹⁰⁴ It is quite well known that the greater the amount of vascular endothelial growth factor (VEGF) present in a cancer, the more rapid the tumor growth. VEGF, produced by a gene isolated by Genentech's Napoleone Ferrara, is critical for the production of blood vessels. Embryos with defective VEGF genes die before birth because of the failure to grow normal

blood vessels, evidence for the role of VEGF as a key player.

Molecular biologists Peter Hirth and Gwen Fyfe of Sugen/Pharmacia Corporation have tried to deactivate the receptor sites of VEGF, whereas Genentech has designed a monoclonal antibody to VEGF that slowed tumor growth in animals by preventing VEGF from docking with its receptor. These antibodies are engineered versions of natural immune system fighters that attack a particular target. Clone systems, a New York company, has also entered the fray with a designed antibody against VEGF that it hopes will be more potent than that of Genentech's. Novartis and Astra-Zeneca are also testing drugs to block VEGF.

This idea of starving tumors by antiangiogenesis has been attributed to Judah Folkman whose effort with Entremed in Rockville, Maryland, targeting angiostatin and endostatin seems less advanced than the VEGF research.

Still, VEGF blockers alone may be inadequate and, therefore, work on blocking mutant genes that avoid growth-inhibitions mechanisms and investigation on genes that may cause cell death or apoptosis are being done. Similarly, Genentech has genetically engineered Herceptin to repress HER 2 protein and to kill cancer cells.

Epidermal growth factor receptors (EGFR) is important for cancer growth.¹⁰⁵ Abgenix Company has manufactured a monoclonal antibody against EGFR by injecting human EGFR into mice to create antibodies. But when the mice antibodies are injected into humans, the latter correctly identifies the mice antibodies as foreign and destroys them before they can fight the cancer.

Abgenix has been able to change and disable the mice genes that make the antibodies. Human genes are then inserted into the mice. These human genes direct the production of human antibodies. The result is the Xenomouse which still recognizes the human protein as foreign, but which responds by making human antibodies acceptable to the immune system of human patients.

Adenoviruses, used to introduce p53, a tumor suppressor gene, have been studied by Introgen Therapeutics. Many cancer cases are

COMPANY	DRUGS	STAGE	ACTION
Genentech	VEGF Antibody	Final Stage Testing for lung and colon cancer	AB against VEGF protein
Pharmacia/Sugen	SU5416	Final Stage Testing for colon cancer	Drug that blocks VEGF receptor
Imclone Systems	IMC 1C11	Early Clinical Tests	AB against VEGF receptor
Astra-Zeneca	AZD6474	About to begin human testing	Drug that blocks VEGF receptor
Novartis	PTK-787	Early human tests on temporary hold	Drug that blocks VEGF receptor
Pharmacia/ Sugen	SU6668	Early human tests	Drug that blocks VEGF receptor

missing a p53 gene or have a defective p53 gene. By the introduction of a functional p53 gene, the cancer associated error in the DNA can be spotted and cell suicide or apoptosis can be triggered, thereby avoiding cancer spread.¹⁰⁶

Withdrawal of Carcinogens

Elimination of carcinogens or irritants may play a role in the regression of cancers, especially if the lesion is still in the preinvasive stages.⁸¹ Some malignancies in the bronchial epithelium have regressed with cessation of smoking. Preinvasive changes in uterine cervical cancer, leukoplakia of the mouth, and carcinoma-in-situ of the bladder or colonic polyps have also undergone regression with removal of irritant factors.

Infection, fever, and vaccine mechanisms

One of the most prominent events mentioned in many cases has been fever or sepsis.^{88,89,90} Infections, fever, or even vaccinations associated with the cancer have wrought beneficial effects frequently associated with the disappearance of the cancer.^{5,14,15,30,42,79} Why this happens is unknown. In most articles, some influence on the immune system is mentioned as affecting the cancer.

Apoptosis, Antibody, Antiangiogenesis and Maturation

Reasons for SR whether through apoptosis,⁸² antibody formation,^{7,82} antiangiogenesis,⁶⁶ maturation of the undifferentiated cells,³⁶ cytotoxic or killing activity in the patient's blood,⁵¹ activation of tumor necrosis factor⁶¹ have all been diligently studied.

Studies have suggested that interleukin-4, a cytokine produced by mast cells and T lymphocytes, can cause growth inhibition in human breast cancer cells by inducing apoptosis.⁹⁷ Programmed cell death (apoptosis) also has been correlated with an increase of a protein labeled BAX, whereas Bcl-2, another protein, has been shown to inhibit apoptosis. This can be exhibited by infecting human cancer cells with an adenovirus expressing the cancer growth suppressor gene, mda-87.⁹⁸ Apoptosis in the prostate is activated by hormone ablation and is under the control of several regulating genes including the tumor suppressor gene p53 and the proto-oncogene bcl-2.⁹⁹

Withdrawal of therapy

Bissods and Kaczmarek⁵⁵ reported a case of SR of prostate cancer after withdrawal of diethylstilbestrol therapy. Since a significant proportion of lymphoproliferation disorders have regression of their disease after methotrexate therapy withdrawal, Salloum, *et al*⁵⁶ have suggested that this fact may have important implications in the management of lymphomas.

Natural killer activity

So-called natural killer activity has been found in the blood of patients with lymphoma,⁵¹ renal cell cancer,¹⁸ neuroblastoma,¹⁹ and histiocytoma.⁵⁴ How this killing activity is initiated and the mechanisms through which it works have not yet been uncovered.

Endocrine factors and hormonal and pregnancy influences

That hormones can influence breast cancer is well known.^{31,34,47} The role of tamoxifen, lactation, pregnancy, estrogen, and cortisone in

their influence on breast carcinomas are excellent examples of the endocrine effect.

Prayer in spontaneous regression of cancer

Recently, Harris,⁶⁸ in a randomized, controlled trial, pointed out the positive outcomes in patients admitted to the coronary care units affected by remote intercessory progress. This appeared to be a confirmation of Bryd's⁷³ study on the beneficial effects of intercessory prayers again in a coronary care unit population. Hirschberg and Barasch [31], in their recent book, suggested that optimistic, positive attitudes and spirituality helped in cancer cures and possibly even with SR. It would be, of course, extremely difficult to prove conclusively a connection between prayers and SR.

In a study by Berlan,⁷⁸ a large percentage of patients attributed their recovery to their prayers and to God.

In case one of this paper, the SR was attributed, by the patient, to the intercession of Father Damien.⁹² Her faith and belief in the benefits of prayer led her to write to the Pope in Rome and to start the process for the canonization or sainthood of Blessed Damien when her bilateral pulmonary liposarcoma metastases all disappeared.

In case two of this paper, the patient prayed to Buddha. According to Tseng⁷⁰ and Chan,⁸⁷ prayers allowed the "chi" or vital energy to flow unrestricted from the body and allowed the mutated cancer cells to mature or differentiate and revert back to a normal state.

It is unknown whether prayers were used in cases 3 and 4 of this manuscript.

Of course, the most famous story of prayers affecting cancer is that of St. Peregrine, the patron saint of cancer.³² When the latter was a young priest, he was scheduled for an amputation because of a cancer of his leg. The night prior to his operation, he prayed fervently, dreamed that he was cured, and, on awakening, he was indeed cured. He was canonized St. Peregrine in 1726.

That prayers influenced the SR's in cases 1 and 2 described in this manuscript can be difficult, if not impossible, to prove. Mention of the connection between SR's and prayers is made as part of the discussion because of the fairly large number of writings in the review of the literature and for the completion's sake.⁹⁴

Comment

Why SR occurred in the above 4 reported cases is unknown. Could it be the infections or inflammation or necrosis in the first 3 cases? The 4th case of the ruptured hepatocellular carcinoma and cirrhosis of the liver with the emergency right hepatic lobectomy did not have sepsis.

In the case of the metastatic pleomorphic liposarcoma, doxycycline was injected into the left hip seroma cavity. Could it be that the doxycycline, an antibiotic synthetically derived from oxytetracycline, behave similarly as the tetracycline given to the leukemic mice in Huettner's experiment,⁹³ thereby cause a "switching off" of the liposarcoma proliferation? But the doxycycline was given 6 months before the metastases appeared.

It should be emphasized that the four cases of SR described in this article were well documented, well diagnosed, and histologically proven, and without any treatment or treated inadequately to exert a cure as in case 4 when only an emergency right hepatic lobectomy was done and gross cancer was left in the left lobe. Yet all cases

showed complete and permanent disappearance of all of the cancers. Thus, they easily met the criteria as set forth by Everson and Cole.¹

The author also had a fifth case of a 93-year-old mother of an internist with painless obstructive jaundice due to a hard mass, presumed to be a cancer, in the head of the pancreas. Because of her age and her physical condition, only a bypass with a choledochojunostomy-roux-en-y was done. She survived another 10 years. Unfortunately, no biopsy of the pancreas was done and thus, this case could not be included in this paper as an example of SR because of the lack of histological proof.

Finally, adherence to the title and thesis of this paper would suggest that the definition of complete spontaneous regression of cancer be modified to state that it is the disappearance of all of a well diagnosed malignancy in the absence of any treatment or in the presence of therapy considered inadequate to exert a significant influence on the neoplasm. Regressions should last at least one year.

Conclusion

Four cases of complete spontaneous regression of cancers, a review of the literature, and a discussion of various possible mechanisms involved in the disappearance of the malignancies were presented. The four very rare events of SR are interesting because of the sparsity of solid cancers with SR. The metastatic pleomorphic liposarcoma in the lungs and the recurrent squamous cell carcinoma of the esophagus may be the first case reports of their kind.

SR's may be even rarer than previously believed and the incidence may be one per 140,000 cases of cancer rather than the one per 60,000 to 100,000 cancer cases as earlier thought.

Most SR's have been associated with leukemias and lymphomas and, therefore, SR's of solid cancers are rare. The immune system of the patients with SR's may have been influenced in some way by one or more of the variously described mechanisms to enable the body to destroy the cancers. Genetic induction and suppression of cancers have recently been shown to play important roles in cancer. Although immunological processes are stated in the literature to be the most likely cause for SR, recent work has showed that genetic mechanisms may be the more important processes as shown by studies on gene damage, abnormal protein expressions and the correction or inhibition of the offending protein.

Exact pathways have not yet been delineated but various theories have been described. The mystery of SR has not yet been solved but some secrets are beginning to be unlocked.

It may be that the pathway to cancer regressions, spontaneous or otherwise, lies not in the "angel's crown which is Immunity,"¹⁰³ but rather in our genes and in the inhibition, correction, and in the prevention of their abnormal expressions.

Finally the definition of complete spontaneous regression of cancer was modified to state that it is the disappearance of all of a well diagnosed malignancy in the absence of any treatment or in the presence of therapy considered inadequate to exert a significant influence of the neoplasm. Regressions should last at least one year.

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