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REFERENCES

Adams, F. D., (1951). *New Engl. J. Med.*, **244**, 590.
Baker, W. H., and Roth, S. I. (1963). *Ibid.*, **269**, 801.
Clin. Path Conf. (1960). *Brit. med. J.*, **1**, 1632.
Cohen, S. I., Fitzgerald, M. G., Fourman, P., Griffiths, W. J., and De Wardener, H. E. (1957). *Quart. J. Med.*, **26**, 423.
Couch, R. S. C., and Lewis, A. A. G. (1953). *Arch. Middx Hosp.*, **3**, 84.
David, N. J., Verner, J. V., and Engel, F. L. (1962). *Amer. J. Med.*, **33**, 88.
Ellsworth, R., and Howard, J. E. (1934). *Bull. Johns Hopk.*, **55**, 296.
—— and Nicholson, W. M. (1935). *J. clin. Invest.*, **14**, 823.
Fales, F. W. (1953). *J. biol. Chem.*, **204**, 577.
Fanconi, A. and Rose, G. A. (1958). *Quart. J. Med.*, **27**, 463.
Ferris, T., Kashgarian, M., Levitin, H., Brandt. I., and Epstein, F. H., (1961). *New Engl. J. Med.*, **265**, 924.
Fiske, C. H., and Subbarow, Y. (1925). *J. biol. Chem.*, **66**, 375.
Fourman, P., McConkey, B., and Smith, J. W. G. (1960). *Lancet*, **1**, 619.
Gleckler, W. J. (1956). *Ann. intern. Med.*, **44**, 174.
Gutman, A. B., Tyson, T. L., and Gutman, E. B. (1936). *Ibid.*, **57**, 379.
Hänze, S. (1959), *Klin. Wschr.*, **37**, 31.
Horwith, M., Rich, C., Thompson, D. D., and Rasmussen, H. (1961). In *The Parathyroids*, edited by R. O. Greep and R. V. Talmage, p. 415. Thomas, Springfield, Ill.
Howard, J. E. (1962). *Trans. Coll. Phycns Philad.*, **30**, 55.
—— and Meyer, R. J. (1948). *J. clin. Endocr.*, **8**, 895.
Kleeman, C. R., and Cooke, R. E. (1951). *J. Lab. clin. Med.*, **38**, 112.
Leaf, A. (1951). *New Engl. J. Med.*, **245**, 504.
Longcope, W. T., and Freiman, D. G. (1952). *Medicine (Baltimore)*, **31**, 1.
Lucas, P. F. (1960). *Brit. med. J.*, **1**, 1330.
McSwiney, R. R., and Mills, I. H. (1956). *Lancet*, **2**, 862.
Natelson, S. (1951). *Amer. J. clin. Path.*, **21**, 1153.
Nordin, B. E. C. (1960). *Clin. Sci.*, **19**, 311.
Sanderson, P. H. (1952). *Biochem. J.*, **52**, 502.
—— (1959). *Brit. med. J.*, **2**, 275.
Schneider, R. W., and Kammer, H. (1948). *Cleveland Clin. Quart.*, **15**, 82.
Scholz, D. A. (1959). *J. Amer. med. Ass.*, **169**, 682.
—— and Keating, F. R. (1956). *Amer. J. Med.*, **21**, 75.
Solomon, R. B., and Channick, B. J. (1960). *Ann. intern. Med.*, **53**, 1232.
Thomas, W. C., Connor, T. B., and Morgan, H. G. (1958). *J. Lab. clin. Med.*, **52**, 11.
Verner, J. V., Engel, F. L., and McPherson, H. T. (1958). *Ann. intern. Med.*, **48**, 765.
Wallach, S., and Carter, A. C. (1961). *Amer. J. Physiol.*, **200**, 359.
Walter, O. (1951). *Z. ges. inn. Med.*, **6**, 664.
Wenger, J., Kirsner, J. B., and Palmer, W. L. (1957). *Gastroenterology*, **33**, 745.
Wolf, A. V., and Ball, S. M. (1949). *Amer. J. Physiol.*, **158**, 205.
Wrong, O., and Davies, H. E. F. (1959). *Quart. J. Med.*, **28**, 259.

Hodgkin's Disease and Hypogammaglobulinaemia: A Rare Association

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Hypogammaglobulinaemia has been classified into three main groups (*Lancet*, 1962). This classification, though useful, is probably not entirely adequate as knowledge about the condition increases (Fudenberg and Franklin, 1963). The three groups are: (1) a primary congenital abnormality of sex-linked recessive inheritance, practically confined to boys; (2) a primary, acquired disease occurring in adults of both sexes, with evidence that some cases at least involve a genetic factor (Fudenberg and Franklin, 1963; Hoffbrand, 1964); (3) a disease associated with, and presumed to be secondary to, various diseases involving the reticulo-endothelial system.

In the third group, chronic lymphatic leukaemia (Fairley and Scott, 1961), multiple myeloma (Eastham and Yeoman, 1960), and generalized lymphosarcoma (Ultmann, Fish, Osserman, and Gellhorn, 1959) are well recognized as being associated with a relatively high incidence of hypogammaglobulinaemia. Hodgkin's disease is also frequently stated to be responsible for such secondary, acquired hypogammaglobulinaemia (*Lancet*, 1958; 1962; Wolf, 1962). It was surprising, therefore, to be unable to find a single documented case of Hodgkin's disease, with repeated infections attributable to hypogammaglobulinaemia, or with a serum gamma-globulin level reduced to 200 mg./100 ml. or less, the level below which the Medical Research Council Working Party for Hypogammaglobulinaemia accepts a case of the primary disease for inclusion in its trial (Squire, 1960).

The rarity of hypogammaglobulinaemia in Hodgkin's disease may be more apparent than real, and may be due to differences in histological criteria of diagnosis, or to failure to recognize or publish cases. However, since the widespread introduction of electrophoresis, numerous workers have investigated the serum proteins in Hodgkin's disease (Petermann, Karnofsky, and Hogness, 1948; Rottino, Suchoff, and Stern, 1948; Arends, Coonrad, and Rundles, 1954; Cazal, Carli, and Fischer, 1956; Neely and Neill, 1956; Wall, 1958; Teitelbaum, Weiner, and Desforges, 1959; Krasnik and Baranowska, 1959; Goudemand and Foucaut, 1960; Onat and Cooper, 1960; Boggs and Fahey, 1960; Miller, 1962). These workers have examined the serum, often on more than one occasion, from no fewer than 417 cases of Hodgkin's disease, without finding one case with a serum gamma-globulin level approaching 200 mg./100 ml. Wall (1958) specifically mentions the rarity of hypogammaglobulinaemia in Hodgkin's disease compared with the other lymphomas.

Two cases of Hodgkin's disease associated with serum gamma-globulin levels less than 200 mg./100 ml., as measured by a gel-diffusion precipitin method (Gell, 1957), have been seen recently at University College Hospital. They are reported, together with the results of an as yet incomplete study of the immunoglobulins of the apparently healthy first-degree relatives of the two patients.

Case Histories

Case 1

A boy aged 12 was seen in October 1955 with a lump in the neck of one year's duration. He was otherwise well, with no notable past history, except chicken-pox at the age of 5. Biopsy of enlarged cervical lymph glands was performed, and the histological examination showed loss of architecture, a pleomorphic cellular infiltrate, and scanty Reed-Sternberg cells. A diagnosis of Hodgkin's disease was made. In view of his subsequent history, it is interesting to note that one gland sectioned at this time showed a relatively normal structure, with follicular hyperplasia and plasma cells.

Between October 1955 and March 1960 he received nine courses of radiotherapy to enlarged superficial lymph glands and his lumbar

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spine. From December 1958 he was given 5 to 10 mg. prednisone a day. When patchy opacities in both lung fields were discovered in November 1959 he was treated with chlorambucil and, in June 1961, he had cyclophosphamide. Unfortunately, the full details of the radiotherapy and the antimitotic drugs that he received are lost.

In July 1960 fever responded to intravenous nitrogen mustard. Later in the year he had herpes zoster on one buttock, followed by a generalized eruption. In June 1961 he presented with the clinical picture of acute appendicitis. Laparotomy revealed an inflamed caecum, which responded to conservative measures. Shortly afterwards an enlarged testicle was removed and found to be infiltrated with Hodgkin's tissue.

Terminal Illness.—He fell ill again in November 1961 with facial boils and bronchitis, which responded to demethylchlortetracycline only to recur two weeks later. His sputum then yielded *Staphylococcus pyogenes.* Soon afterwards he developed left pleuritic chest pain with a friction rub, and a few days later he became acutely ill with a left-sided tension pneumothorax. This is a recognized complication of what was, almost certainly, a staphylococcal pneumonia during steroid therapy (Olesen and Quaade, 1961).

He was admitted to University College Hospital, where the tension pneumothorax was relieved by aspiration. He had a rash, which had started five days previously as discrete, red-brown maculopapules, which soon vesiculated. These were situated mainly on the face and trunk, and were considered by several observers to be varicella. The family doctor said that they were identical with the lesions of the generalized eruption, associated with the attack of herpes zoster that the boy had had the year before. There was no enlargement of liver, spleen, or superficial lymph glands.

Investigations.—Haemoglobin was 9.9 g./100 ml., and white-cell count 9,000/cmm. (normally differential). There was no protein or sugar in the urine and microscopy was normal. Chest radiograph showed a cavity in the left mid-zone, with persistent opacities in both lung fields. Total serum protein was 4.25 g./100 ml., with a small increase in the alpha 2, and a marked reduction of the gamma-globulin levels on paper electrophoresis. Five grams of gamma-globulin had been given, intramuscularly over 48 hours, before blood was taken for gel-diffusion precipitin estimation of the immunoglobulins. This showed a gamma-globulin level of 280 mg./100 ml., with a gamma-macroglobulin (beta 2M) level of 3% of a standard "normal" serum. It is estimated that before treatment the gamma-globulin level was 180 mg./100 ml. (Gitlin, Gross, and Janeway, 1959). The result of biopsy of the skin lesions was considered to be very suggestive of varicella. Vesicular fluid failed to grow the herpes simplex virus; unfortunately, isolation of the varicella-herpes zoster virus was not technically feasible.

Progress.—The skin lesions increased in size to give necrotic ulcers, 5 cm. in diameter. At the time there was a very real risk of a smallpox epidemic, and, before the hypogammaglobulinaemia had been diagnosed, the patient was vaccinated. This produced typical vaccinia gangrenosa. The patient's general condition deteriorated in spite of antibiotics and gamma-globulin given as described above. He died seven weeks after admission.

Necropsy.—There was severe bilateral bronchopneumonia, with an old abscess cavity in the left lung. Histological examination showed no evidence of Hodgkin's tissue or tuberculosis, but a culture for tuberculosis later proved positive. Hodgkin's tissue was found in the kidneys, the remaining testis, and the few enlarged abdominal lymph glands. The marrow was hypocellular, and the liver and spleen, though about twice normal size, showed no recognizable Hodgkin's tissue, reticulum cell hyperplasia, or granulomatous process (Martin, 1962). There was no evidence of gastrointestinal involvement, macroscopically or on section. There were scattered plasma cells in all tissues examined.

Comment.—Atypical varicella is well recognized in patients on steroids, especially those with leukaemia (Finkel, 1961). However, this patient had no fewer than three attacks of widespread eruption, due to the varicella-herpes zoster virus, the last of which progressed to gangrenous ulcers. It is suggested that the hypogammaglobulinaemia was responsible for this clinical feature. Recurrent varicella has been previously described in hypogammaglobulinaemia (Gitlin, *et al.*, 1959).

Vaccinia gangrenosa, from which the patient suffered at the end of his life, is a well-recognized complication of hypogammaglobulinaemia (White, 1963). The acute typhlitis, which the patient had 18 months before he died, may have been an acute manifestation of the more chronic gastrointestinal changes, known to occur in idiopathic hypogammaglobulinaemia, which present as chronic diarrhoea or frank steatorrhoea (Cooke, Weiner, and Shinton, 1957).

Case 2

An electrician was first seen at University College Hospital in 1932, at the age of 21, complaining of a lump that he had had in the left side of his neck for a few months. He gave a history of meningitis at the age of 5, and pneumonia at the age of 14. He was found to have a mass of enlarged lymph glands in the left side of his neck, with enlarged glands in both axillae and the right side of his neck. He also had a nasopharyngeal mass, which was thought to be adenoidal. A blood count was normal. Biopsy of the mass was thought to show a malignant "endothelioma." He had a block dissection of the left side of his neck, followed by the insertion of radium needles.

In 1933 he was readmitted with a severe infection of an extensive nasopharyngeal mass, which subsided spontaneously. In 1946 he had an abscess in the left parotid region from which pneumococci were isolated. A further abscess occurred at the same site in 1953.

In 1954 he had a severe pneumonia after which he developed chronic cough and sputum, with exacerbations of increasing frequency. He was seen again in 1958 because of his chest symptoms. His only abnormal physical signs at this time were old operation scars and bilateral basal rales. A radiograph of the chest was normal and a bronchogram showed changes of chronic bronchitis only.

He was admitted to hospital in July 1962, now aged 52, complaining of tiredness, dyspnoea, cough, and yellow sputum for six months. In addition to the signs noted in 1958, he was found to be anaemic, with an enlarged liver, 8 cm. below the costal margin, and an enlarged spleen, 2 cm. below the umbilicus. He also had enlarged inguinal lymph glands.

Investigations.—Review of the histology of the 1932 operation showed merely chronic lymphadenitis, with a normal follicular structure and plasma cells. There was no evidence of a malignant process. Haemoglobin was 7.9 g./100 ml. with routine haematological investigations suggesting a haemolytic state, confirmed by radiochromium studies (Hoffbrand, 1964b). White-cell count showed 4,700/c.mm. (myelocytes 1.5%), platelets normal. There was no protein or sugar in the urine, and microscopy was normal. Total serum protein was 6.2 g./100 ml., with paper electrophoresis showing a small reduction in the albumin, a small increase in the beta-globulin, and a marked reduction in the gamma-globulin levels. Gel-diffusion precipitin estimation gave a serum gamma-globulin level of 70 mg./100 ml., a gamma-macroglobulin (beta 2M) level of 12%, and a gamma-1A (beta 2A) level of 0.4% of a standard "normal" serum. Immuno-electrophoresis showed, in addition, slight reductions in siderophilin, caeruloplasmin, and certain alpha-2-globulins. The patient was blood group-A, with a weak anti-B isohaemagglutinin titre of 1/4 (control 1/128). Sternal marrow aspiration showed lymphocytes, with occasional late normoblasts, while radiograph of the chest showed widening of the superior mediastinum. Biopsy of the inguinal gland revealed classical Hodgkin's disease.

Treatment and Progress.—Abdominal radiotherapy, prednisone, and antibiotics produced a marked symptomatic improvement. When he was readmitted in November 1962 after a relapse of his presenting symptoms, renal glycosuria was noted. A urine amino-acid chromatogram showed a gross aminoaciduria of "central cluster" pattern. An indole chromatogram showed moderate amounts of kynurenine, 3-hydroxykynurenine, xanthurenic acid, and three fluorescing unknowns. None of these intermediaries in tryptophan metabolism is present in normal urine. His general condition deteriorated progressively until his death in hospital in April 1963 with a severe chest infection.

Necropsy—There was widespread bilateral bronchopneumonia. The spleen was about three times the normal size and infiltrated with Hodgkin's tissue, as were enlarged cervical, axillary, para-aortic, and iliac lymph glands. The liver showed extreme focal biliary retention, due to fibrous strictures from healed Hodgkin's tissue involving intra-hepatic bile ducts. Plasma cells were seen in several sections.

Comment.—The lymphadenopathy and gross adenoidal hypertrophy found in this patient in 1932 are suggestively like the findings in some cases of idiopathic acquired hypogammaglobulinaemia (Good, Kelly, Rötstein, and Varco, 1962). He also had repeated infections. The picture, while by no means diagnostic of classical hypogammaglobu-

linaemia, is thought to be suggestive of some long-standing deficiency of bacterial immunity. The aminoaciduria, found terminally, remains unexplained, though the previous abdominal radiotherapy may have contributed to it (Katz and Hasterlik, 1955).

Family Studies

There is no history in the family of either case of an increased tendency to infections, of lymphoma, or of disorders of connective tissue (Wolf, 1962 ; Fudenberg and Franklin, 1963).

Family of Case 1

Immunoelectrophoresis showed the following abnormalities of the immunoglobulin levels:

	Age	Marked Reduction Beta 2A	Reduction	
			Gamma	Beta 2M
Mother	50	+	+	
Sister	29	+		+
Brother	25	+		+
Sister	8	+	+	

Gel-diffusion precipitin estimation confirmed the low beta 2A levels.

Family of Case 2

Gel-diffusion precipitin estimation gave the following results:

	Age	Gamma Globulin (mg./100 ml.)	(% of a Standard "Normal" Serum)	
			Gamma Macroglobulin	Gamma 1A
Daughter*	22	960	175	87
Brother*	47	1,120	250	100
„ *	36	1,600	350	75
„	56	1,280	600	100
„	42	1,600	200	87
„	40	1,280	100	100
„	37	1,600	175	100
Sister	39	1,280	1,000	37

The undoubted abnormalities are the raised gamma-macroglobulin (beta 2M) levels of several of the brothers and the sister. Cytogenic studies (Dr. W. McDiarmid) showed normal chromosomal patterns in the relatives examined (Elves and Israëls, 1963).

Recent reports of an association of chromosome abnormalities and dysproteinaemias, such as macroglobulinaemia (Elves and Israëls, 1963), suggested that chromosome studies in these families would be of especial interest.

Discussion

Though antimitotic drugs, radiotherapy, and steroids may have contributed to the gamma-globulin deficiency of Case 1 (Taliaferro, 1957), this was not possible in Case 2, whose hypogammaglobulinaemia was diagnosed before treatment was started.

The quantitative abnormalities of the immunoglobulins of certain relatives suggest that both cases had so-called "atypical hypogammaglobulinaemia (Fudenberg and Franklin, 1963 ; Burtin, 1963). The later development of Hodgkin's disease in patients with genetically determined abnormalities of immunoglobulin synthesis may well be more than mere coincidence. Thus leukaemia has been found late in the course of congenital hypogammaglobulinaemia (Videbaek, 1962 ; Good *et al.*, 1962). The latter authors suggest that this occurrence might favour the hypothesis of an infectious aetiology of the leukaemia. It might also be argued that the abnormal synthesis of immunoglobulin and the malignant process are different expressions of a basic genetic defect. Such considerations might also be profitably applied to chronic lymphatic leukaemia, in which hypogammaglobulinaemia is relatively common and usually regarded as secondary to the leukaemia (Fairley and Scott, 1961).

The rarity of hypogammaglobulinaemia in Hodgkin's disease must be stressed. Family studies should be done when these two conditions are found together. Only in the absence of evidence of a prior defect of immunoglobulin synthesis can the hypogammaglobulinaemia be attributed simply to the Hodgkin's disease. However, though a familial defect in the synthesis of gamma-globulin was probably the most important single factor in determining the development of hypogammaglobulinaemia in these patients, one cannot exclude a contribution by the Hodgkin's disease itself.

Summary

Two cases of Hodgkin's disease associated with hypogammaglobulinaemia are reported. They are believed to be the first recorded cases. One patient, a youth, had otherwise typical Hodgkin's disease, complicated terminally by vaccinia gangrenosa and progressive ulcerated skin lesions, due to a third varicella infection. The other patient, a 52-year-old man, had a history of hypertrophy of lymphatic tissue and repeated infections, attributed to a long-standing immunological deficiency, and preceding the development of classical Hodgkin's disease. Relatives of both cases have quantitative abnormalities of their immunoglobulins. This strongly suggests that these patients had "atypical hypogammaglobulinaemia." The significance of the association of such an abnormality of immunoglobin synthesis with Hodgkin's disease is briefly discussed.

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References

Arends, T., Coonrad, E. V., and Rundles, R. W. (1954). *Amer. J. Med.*, **16**, 833.
Boggs, D. R., and Fahey, J. L. (1960). *J. nat. Cancer Inst.*, **25**, 1381.
Burtin, P. (1963). Personal communication.
Cazal, P., Carli, G., and Fischer, J. (1956). *Presse méd.*, **64**, 184.
Cooke, W. T., Weiner, W., and Shinton, N. K. (1957). *Brit. med. J.*, **1**, 1151.
Eastham, R. D., and Yeoman, W. B. (1960). *Acta med. scand.*, **166**, 241.
Elves, M. W., and Iraëls, M. C. G. (1963). *Brit. med. J.*, **2**, 1024.
Fairley, G. H., and Scott, R. B. (1961). Ibid., **2**, 920.
Finkel, K. C. (1961). *Pediatrics*, **28**, 436.
Fudenberg, H., and Franklin, E. C. (1963). *Ann. intern. Med.*, **58**, 171.
Gell, P. G. H. (1957). *J. clin. Path.*, **10**, 67.
Gitlin, D., Gross, P. A. M., and Janeway, C. A. (1959). *New Engl. J. Med.*, **260**, 72.
Good, R. A., Kelly, W. D., Rötstein, J., and Varco, R. L. (1962). In *Progress in Allergy*, Vol. 6, p. 187, edited by P. Kallos and B. H. Waksman. Karger, Basle, New York.
Goudemand, M., and Foucaut, M. (1960). *Lille méd.*, **5**, 394.
Hoffbrand, B. I. (1964). *Postgrad. med. J.*, **40**, 209.
—— (1964b). *Brit. J. Cancer.* Accepted for publication.
Katz, E. J., and Hasterlik, R. J. (1955). *J. nat. Cancer Inst.*, **15**, 1085.
Kraśnik, W., and Baranowska, B. (1959). *Pol. Arch. weteryn.*, **29**, 443.
Lancet, 1958, **1**, 1317.
Ibid., 1962, **2**, 234.
Martin, N. H. (1962). *Proc. roy. Soc. Med.*, **55**, 398.
Miller, D. G. (1962). *Ann. intern. Med.*, **57**, 703.
Neely, R. A., and Neill, D. W. (1956). *Brit. J. Haemat.*, **2**, 32.
Olesen, K. H., and Quaade, F. (1961). *Lancet*, **1**, 535.
Onat, A., and Cooper, T. (1960). *Blood*, **15**, 114.
Petermann, M. L., Karnofsky, D. A., and Hogness, K. R. (1948). *Cancer*, **1**, 109.
Rottino, A., Suchoff, D., and Stern, K. G. (1948). *J. Lab. clin. Med.*, **33**, 624.
Squire, J. R. (1960). *Acta haemat. (Basel)*, **24**, 99.
Taliaferro, W. H. (1957). *Ann. N.Y. Acad. Sci.*, **69**, 745.
Teitelbaum, J. I., Wiener, J., and Desforges, J. F. (1959). *J. Lab. clin. Med.*, **53**, 535.
Ultmann, J. E., Fish, W., Osserman, E., and Gellhorn, A. (1959). *Ann. intern. Med.*, **51**, 501.
Videbaek, A. (1962). Personal communication.
Wall, R. L. (1958). *Arch. intern. Med.*, **102**, 618.
White, C. M. (1963). *Lancet*, **1**, 969.
Wolf, J. K. (1962). *New Engl. J. Med.*, **266**, 473.