Chloracne is the most sensitive and specific marker for a possible dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin) intoxication. It is clinically characterized by multiple acneform comedone-like cystic eruptions mainly involving face in the malar, temporal, mandibular, auricular/retroauricular regions, and the genitalia, often occurring in age groups not typical for acne vulgaris. Histopathology is essential for a definite diagnosis, which exhibits atrophy or absence of sebaceous glands as well as infundibular dilatation or cystic formation of hair follicles, hyperplasia of epidermis, and hyperpigmentation of stratum corneum. The appearance of chloracne and its clinical severity does not correlate with the blood levels of dioxins. Pathogenesis of chloracne remains largely unclear. An "aryl hydrocarbon receptor"-mediated signaling pathway affecting the multipotent stem cells in the pilosebaceous units is probably the major molecular mechanism inducing chloracne. Chloracne is resistant to all the available treatment modalities used to treat acne. The aim of treatment is to lower or to eliminate the accumulated dioxins in the body at the very beginning of intoxication, e.g., by using dioxin-chelating substances such as synthetic dietary fat substitutes. The problem of dioxin contamination and its potential health hazards should be taken seriously in the wave of industrial globalization in the twenty-first century. Clinicians, especially dermatologists, are in the forefront of early diagnosis of dioxin intoxication.

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made by cooperation between dermatologists K.H. Schulz and J. Kimmig with the chemist G. Sorge in Hamburg, Germany, who investigated patients with atypical acne in a chemical plant.12 Due to its extensive long-term developmental and neurological toxicity, hormonal and immunologic disruption as well as cancer promotion, the production of polychlorinated biphenyls has been prohibited by the Stockholm Treaty on Persistent Organic Pollutants passed in 2004.13 The most recent sensational case report of chloracne incident was about the TCDD poisoning of Viktor Andriyovych Yushchenko, a former president of Ukraine in late December 2004.14

Clinical picture of chloracne

The typical manifestation of chloracne begins with multiple acneiform comedone-like lesions that may further form inflammatory nodules/cysts and noninflammatory straw-colored “epidermal” cysts, involving preferentially the face in the periorbital overlying os zygomaticum, malar, temporal, mandibular and auricular/retroauricular regions (Figure 2). Concurrence with comedones and some inflammatory papulopustules is usually observed in adults but it is unclear if these are real acne lesions. Any part of the body, including the genitalia and the limbs, can be affected and atrophic scar is a common late sequela.10,15 Differentiation from acne vulgaris in the early phase of outbreak can be challenging. The simultaneous appearance of cutaneous hyperpigmentation and conjunctival discharge (defective meibomian glands) is a useful diagnostic sign. Chloracne can develop soon, e.g., in a few weeks, after exposure to chloracnegens.16 In general, the clinical manifestation is not very diagnostic and a histologic examination is required in isolated suspected cases. A detailed medical history, especially an inquiry about clustering of similar cases in the workplaces or at home, is necessary. Occurrence of monomorphous acneiform lesions beyond the “acne age,” e.g., in the childhood, should also raise special attention, because the chloracnegens especially dioxins can pass via placenta or breast milk and induce chloracne without direct exposure.17

Histopathology of chloracne

The histopathology of chloracne is characterized mainly by miniature to absent sebaceous glands, accompanied by hyperplasia of epidermis and hyperpigmentation of stratum corneum. In addition, follicular hyperkeratosis with orthokeratosis, infundibular dilatation, and infundibular cysts can be detected. Occasionally, inflammatory infiltrate, solar elastosis, and thinning of the follicular wall with cicatricial atrophy can be found.18 The histopathologic features of chloracne lesions have been systematically evaluated both in human volunteers,19 in hairless mice model,20 and in ex vivo human skin studies.21 In early lesions, the epithelial cells of the outer root sheath formed the wall of the proximal portion of the infundibulum resulting in dilatation of the proximal infundibulum. The walls of the sebaceous glands are thickened and merged with the follicular infundibular wall. Hyperplasia of the epidermal keratinocytes with incomplete keratinization is indicated by a thick, parakeratotic cell layer surrounding a mass of keratinized epidermal cells, which begins a proximal filling of the infundibulum. In later stage lesions,
almost all of the pilosebaceous units are involved. A definite diminution of the sebaceous glands with reduced numbers of cells and reduced size of sebaceous lobules with in a normal appearance can be detected. Lesions at the later stage consist of small comedones with nearly all of the vellus hair follicles with a thickening of the outer root sheath, dilated infundibula filled with sebum, and absence of sebaceous lobules. In addition, a few cases of chloracne were observed with numerous tiny infundibular cysts instead of comedones representing the major lesions of chloracne without squamous metaplasia of the sebaceous glands or ducts.\textsuperscript{30,22}

**Pathogenesis of chloracne**

Pathogenesis of chloracne remains incompletely understood. With the disappearance instead of hypertrophy of sebaceous glands, chloracne is actually not acne and the term is a misnomer.\textsuperscript{1} The minimum threshold value of dioxin inducing chloracne is poorly defined. On the other hand, the clinical severity of chloracne is not always correlated with the blood level of dioxin.\textsuperscript{23} In general, chloracne is absent when serum chloracnegens below 1,000 pg TEQ (TCDD-toxic-equivalent)/g lipid weight but can be observed with TEQ/g above 10,000 pg/g lipid weight.\textsuperscript{2} However, chloracne can occur even when serum-TEQ values are in the normal range, i.e., 5.39 pg TEQ/g lipid weight.\textsuperscript{18} Due to its high lipophilicity, the median half-life of dioxins was estimated to be 2.9 years in the first 15 years after intoxication and 7.7 years in the next stage of 15 years.\textsuperscript{24} As the major histopathologic characteristic of chloracne is hyperplasia of epidermal cells with atrophy and replacement of the sebaceous glands and ducts by keratinized epithelial cells, this indicates different epithelial structures in the skin may respond differentially to chloracnegens. Earlier studies have reported that sebaceous glands are replaced by keratinized epithelial cells because sebaceous glands undergo squamous metaplasia and keratinization in patients with chloracne.\textsuperscript{25} However, as epidermal progenitor cells in the bulge region of the hair follicle give rise to multiple skin lineages, including hair follicles, sebaceous glands, and the interfollicular epidermis,\textsuperscript{26} it is hypothesized that chloracnegen-induced transformation of the pilosebaceous unit is driven by activation and accelerated exit of cells from the stem cell compartment coupled with a shift from a pilosebaceous differentiation pattern to an epidermal one.\textsuperscript{27} This may result in imbalance between early multipotent cells commitment and their preferential differentiation along an epidermal lineage with consequent diminution of sebaceous gland and lower hair follicle portion along with prominent infundibular hyperplasia and hyperkeratinization.

Mechanisms of the effects of dioxins on keratinocyte differentiation are still controversial. Topical application of TCDD in adult hairless mice resulted in hyperkeratinization and induction of mouse dermal cyst, whereas the interfollicular epidermis was not affected.\textsuperscript{28} Exposure of murine fetuses in utero to TCDD led to an accelerated terminal differentiation of fetal skin.\textsuperscript{29} A survey of 23 cell lines displayed no changes in morphology, viability, or growth patterns following treatment with TCDD.\textsuperscript{30} Furthermore, TCDD caused the acceleration of differentiation of a spontaneously immortalized human keratinocyte cell line in a three-dimensional skin equivalent model as determined by morphologic characterization and by immunohistochemistry for several differentiation-specific protein markers. Neither an influence on proliferation nor an induction of apoptosis was observed.\textsuperscript{31} TCDD was found to impair differentiation of normal human epidermal keratinocytes in a skin equivalent model.\textsuperscript{32} Thus most of the studies proved that TCDD exerts profound effects on keratinocyte differentiation in vitro in organotypic cultures but not in monolayer cultures. A recent in vitro study using normal human epidermal keratinocytes showed a TCDD-mediated aryl hydrocarbon receptor (AhR)-dependent acceleration of differentiation and increase in gene expression of several prodifferentiation genes, including filagrin and small proline rich protein 2, indicating the epidermal permeability barrier is also a functional target of the TCDD-activated AhR.\textsuperscript{33}

As the differentiation of sebocytes is severely affected following dioxin exposure in vivo and markedly reduced sebum levels with skin xerosis is an important clinical feature of chloracne,\textsuperscript{34} the effects of dioxins on sebaceous glands are especially interesting and important. TCDD exhibits an inhibitory effect on lipid metabolism in laboratory rodents and humans and induces clinically a wasting syndrome.\textsuperscript{35} The use of animal models such as that of the rabbit ear,\textsuperscript{36} meibomian glands of primates,\textsuperscript{37} and hairless mice has shown that miniaturization of sebaceous glands is noted following TCDD exposure.\textsuperscript{32} It has recently been proven that TCDD decreased lipogenesis and affected differentiation of human sebaceous gland cells by switching the sebaceous into a keratinocyte-like differentiation in cultured SZ95 sebocytes and in human skin maintained ex vivo.\textsuperscript{21}

Most of the effects of TCDD in humans and animals appear to be mediated by the AhR signaling pathway, a member of the basic-helix-loop-helix period-ARNT-single-minded (Per-ARNT-Sim) family of dimeric transcription factors.\textsuperscript{38} AhR was previously found to be expressed and activated in human keratinocytes and skin fibroblasts as well as in human sebaceous glands and human immortalized SZ95 sebocytes.\textsuperscript{21,39,40} In the skin lesions of chloracne patients exposed to dioxin, there was an activation and upregulation of p- epidermal growth factor receptor EGFR (EGFR), p-mitogen-activated protein kinase, and CK17 in all chloracne tissues but not in the controls, while transglutaminase 1 showed distinct distribution patterns.\textsuperscript{31} Furthermore, an increase in the dioxin-independent transcriptional activity of the AhR has recently been demonstrated in a Drosophila model to be also responsible for the in vivo dioxin toxicity.\textsuperscript{32}

The specific histologic changes of chloracne can be rationally explained by the hypothesis based on stem-cell theory. Downstream molecular targets of AhR are versatile including influence of classical xenobiotic metabolizing enzymes (such as CYP1A1 and CYP1A2), interleukin-1\(\beta\), tumor growth factors, c-Myc, EGFRs, and B lymphocyte maturation protein 1 (Blimp1, a negative regulator of c-Myc, reported in sebocytes recently).\textsuperscript{40} Among these molecular targets of AhR, c-Myc and Blimp1 are supposed to play an important role in modulating directional differentiation of epidermal progenitor cells and be a potential important target linkage between specific TCDD-induced skin pathology and the stem-cell differentiation changes in the skin. Activation of c-Myc favors differentiation along the lineages of the interfollicular epidermis and sebaceous gland, and it results in the appearance of groups of differentiated sebocytes within the interfollicular epidermis.\textsuperscript{41} Inactivation of c-Myc results in hypoplasia of the sebaceous glands.\textsuperscript{42} Loss of Blimp1 results in the elevation of c-Myc expression and hyperplasia of the sebaceous glands.\textsuperscript{43} Taken together, TCDD/AhR/ARNT/Blimp1 and CYP1A1/c-Myc pathways may very likely be the proposed signaling pathways of TCDD on skin stem-cell progenitors, leading to TCDD-induced abnormal differentiation of sebaceous gland (Figure 3).\textsuperscript{21}

**Treatment of chloracne**

Although some individual reports showed that retinoids,\textsuperscript{46,47} dermabrasion, and light electrodesiccation may be useful in the treatment of chloracne,\textsuperscript{48} chloracne actually appears to be resistant to all tested forms of treatment.\textsuperscript{23,49} Therefore, the only way to manage chloracne is to prevent exposure to chloracnegens.\textsuperscript{45} Once exposure happens, affected individuals should be removed from...
increase in the rate of excretion of labeled compound,51 which combined dietary olestra and caloric restriction causes a 30-fold (Wiley-Blackwell, New Jersey, USA).

Figure 3 Proposed signaling pathway of 2,3,7,8-tetrachlorodibenzo-p-dioxin activity in human sebocytes. Reprinted with permission from Experimental Dermatology (Wiley-Blackwell, New Jersey, USA).

50 Exposure sites and elimination of accumulated chloracneogens from the body should be performed. Recently, a synthetic dietary fat substitute, known as olestra, could bind to chloracneogens and accelerate their fecal excretion. A further study has showed that combined dietary olestra and caloric restriction causes a 30-fold increase in the rate of excretion of labeled compound, which may be a prospective therapeutic method in the future.

Conclusions

The rash globalization and boosting of economic growth, especially in the newly industrialized countries, with improper manufacturing, handling and disposal of, for example electronic waste, may well lead to the propagation, accumulation, and augmentation of the long-lasting toxicity of dioxins, consequently resulting in potential serious threatening health hazards. More than 110 years after its first description, chloracne remains the most sensitive and specific clinical indicator of systemic poisoning by dioxins and other polyhalogenated (poly-chlorinated) aromatic hydrocarbons. Since the clinical diagnosis of chloracne without histopathology may not be straightforward and the laboratory quantification of dioxin level is intricate, clinicians, particularly dermatologists, should keep in mind the possible encounter with chloracne in their daily practice. A better understanding of the pathogenesis of chloracne may help in the development of more specific and effective treatments.

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